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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	56

Application Number	09/106,172
Filing Date	6/26/98
First Named Inventor	Tully
Art Unit	1614
Examiner Name	Frederick Krass
Attorney Docket Number	ROS1997-0601-US

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  1. Application for Extension of Patent Term Under 35 U.S.C. 156 plus Exhibits A - E
  2. Check #043462 for the amount $1,120.00
  3. Postcard

Remarks

Additionally enclosed are four copies of this submission.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Savient Pharmaceuticals, Inc.		
Signature	Peter Tu		
Printed name	Peter Tu		
Date	6 - December - 2005	Reg. No.	43,207

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	Debra Rosenbaum		
Typed or printed name	Debra Rosenbaum	Date	12/6/05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Roger Edward Tully		
Serial No.:	09/106,172	Filed:	June 26, 1998
Patent No.:	6,127,425	Issued:	October 3, 2000
Art Unit:	1614	Examiner:	Frederick Krass
Title:	ORAL LIQUID MEDICINE SOLUTION		

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Mail Stop: Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Applicant, Savient Pharmaceuticals, Inc. ("Savient"), the assignee of record of U.S. Patent No. 6,127,425 (the '425 patent), hereby submits this application for an extension of the term of the '425 Patent pursuant to 35 U.S.C. § 156 and 37 C.F.R. 1.740, based on NDA 21-807. Five copies of this application, including exhibits, are being submitted herewith (in accordance with MPEP 2753 and in compliance with 37 C.F.R. § 1.740(b)). Any fees relating to this application may be charged to Deposit Account No. 50-0832; and Applicant hereby authorizes the Commissioner to charge any fees to the aforementioned deposit account.

1. Complete Identification of the Approved Product (37 CFR 1.740(a)(1))

The approved product is Soltamox™ solution, which is a tamoxifen citrate solution for oral administration. Each 5 mL dose contains 15.2 mg of the active ingredient, tamoxifen citrate, and the following inactive ingredients: ethanol, glycerol, propylene glycol, sorbitol solution (70% w/w sorbitol in water), licorice flavor, aniseed flavor and purified water. The chemical name for tamoxifen citrate is (Z)2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethyl-ethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1). The CAS Number is 54965-24-1. The molecular weight is 563.62; the pKa′ is 8.85. The equilibrium solubility in water at 37°C is 0.5 mg/mL; and in 0.02 N HCl, it is 0.2 mg/mL.

The chemical formula is $C_{26}H_{29}NO \cdot C_6H_8O_7$; and tamoxifen citrate has the following structure:

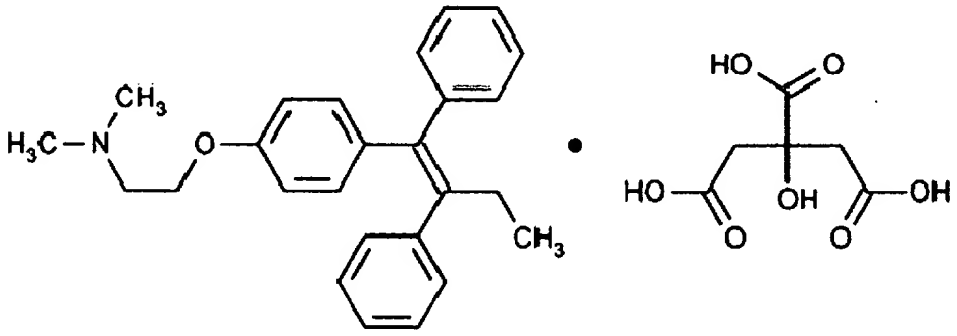

Figure 1

2. **Complete Identification of the Federal Statute Under Which Regulatory Review Occurred (37 CFR § 1.740(a)(2)**

Regulatory permission to market SOLTAMOX™ oral tamoxifen citrate solution was granted under 21 U.S.C. § 355(b)(2) (section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act).

3. **Identification of the Date on Which the Product Received Permission for Commercial Marketing (37 CFR § 1.740(a)(3)**

Regulatory approval for SOLTAMOX™ oral solution (based on NDA 21-807) was granted on October 29, 2005; a copy of the approval letter is attached hereto as Exhibit A.

4. **Identification of Each Active Ingredient and Statement of When the Active Ingredient Was Approved for Commercial Marketing (37 CFR § 1.740(a)(4)**

The sole active ingredient in the approved product is tamoxifen in the form of its citrate salt. An NDA for an oral tablet form (10 mg dose) of this active ingredient was first approved (pursuant to 21 USC § 355(b)(1)) before January 1, 1982. The NDA holder (AstraZeneca) received approval for use of its tamoxifen citrate product for use in treating metastatic breast cancer in men and women, and in treating node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary treatment and breast irradiation.

5. **Statement That Application Is Being Submitted Within Sixty-Day Period (37 CFR 1.740(a)(5))**

This application is being submitted within the sixty-day period specified by 37 CFR § 1.720(f). The last day on which this application could be filed is December 28, 2005; and thus this application is timely filed.

6. Complete Identification of the Patent (37 CFR 1.740(a)(6))

The patent for which patent term extension is sought is U.S. Patent No. 6,127,425, which names Roger Edward Tully as the inventor. The '425 patent issued on October 3, 2000, from U.S. Patent Application Serial No. 09/106,172. The '425 patent, unless its term is extended, will expire on June 26, 2018.

7. Copy of the Patent for Which Extension Is Being Sought (37 CFR 1.740(a)(7))

A copy of the '425 patent is attached hereto as Exhibit B.

8. Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments or Reexamination Certificates (37 CFR 1.740(a)(8))

A copy of the maintenance fee payment record is enclosed herewith as Exhibit C. No disclaimers or certificates of correction have been filed; and no reexamination certificate has been issued with respect to the '425 Patent.

9. Statement That the Patent Claims the Approved Product or Method of Manufacturing the Approved Product, and a Showing That Demonstrates the Manner in Which At Least One Such Patent Claim Reads on the Approved Product or Method of Manufacturing the Approved Product (37 CFR 1.740(a)(9))

Claims 1-6 and 10, if properly construed, claim the approved product literally and/or under the doctrine of equivalents. Claims 7-9 and 11, if properly construed, claim the method of manufacturing the approved product literally and/or under the doctrine of equivalents.

The following chart shows the manner in which claim 1 reads on the approved product.

Claim 1	**Approved Product**
A pharmaceutical preparation which provides a dosage form of Tamoxifen,	The approved product is a pharmaceutical preparation which provides a dosage form of tamoxifen.
wherein the dosage form comprises at least 1.5 mg/ml of Tamoxifen Citrate,	The dosage form for the approved product contains 3.04 mg/ml of tamoxifen citrate.
in the absence of a complexing agent,	The approved product does not contain a complexing agent.
in a pharmaceutically acceptable solution which is administered orally.	The approved product is a pharmaceutically acceptable solution which is administered orally.

The following chart shows the manner in which claim 7 reads on the method for manufacturing the approved product.

Claim 7	**Approved Product**
A process for the preparation of the solution according to claim 2, comprising	The approved product is a solution according to claim 2 (i.e., is a solution comprising "(a) from about 10% to 20% by weight of ethanol; (b) from about 10% to 60% by weight of glycol; and (c) water in a volume percentage adding up to 100% by volume."
dissolving the Tamoxifen Citrate in a mixture of the ethanol and glycol components, and	In the commercial manufacturing process, tamoxifen citrate is dissolved in a mixture of ethanol and glycol components (i.e., propylene glycol and glycerol).
then adding the water component and any other additives.	In the commercial manufacturing process, water and additives are then added.

10. Statement of Relevant Dates and Information Pursuant to 35 USC § 156(g) (37 CFR 1.740(a)(10))

(A) Effective Date of IND

The effective date for the IND for the approved product is January 16, 2004; and the IND number for the approved product is IND 67,993.

(B) Date of Initial Submission of NDA

The NDA for the approved product was initially submitted on December 23, 2004; and the NDA number for the approved product is 21-807.

(C) NDA Approval Date

The NDA for the approved product was approved on October 29, 2005.

11. Brief Description Significant Activities Undertaken by the Marketing Applicant During the Applicable Regulatory Review Period (37 CFR 1.740(a)(11))

(A) IND Activities

A list of significant activities undertaken by the marketing applicant in preparation for filing the IND and during the pendency of IND 67,993 is provided in Table 1 below:

DATE	DESCRIPTION
10/27/05	General Correspondence re: Change in Contact Person at Savient; new contact person is Murad Husain.
1/10/05	Annual report covering time period January 15, 2003 to October 31, 2004.
06/29/04	Protocol Amendment. Serial #004. New investigator-Oberstein.
06/09/04	Protocol Amendment # 4 for C0501, and protocol C0501-2 for re-challenging study. Serial #003.
05/04/04	E-mail re: carton and container labels
04/12/04	Protocol Amendment. Serial #002. New investigator and Clinical information Amendment.
03/23/04	FDA Telephone Call: Christy Cottrell (Consumer Safety Officer) to discuss the use of the Clinical Trials Databank.
03/23/04	Received Letter from FDA re: IND application; approval to proceed with proposed study.
02/09/04	Received Acknowledgement Letter for Change in Protocol submission.
02/03/04	Protocol Amendment. Serial #001: Change in Protocol. Amendment 1
01/14/04	Received Fax from FDA re: comment regarding administration of Soltamox™; study may proceed.
01/02/04	Email to/from D. Pease stating that the IND clock started on December 15, 2003.
12/30/03	Received Acknowledgement Letter for Original IND submission.
12/16/03	Email to D. Pease with copy of original IND cover letter.

DATE	DESCRIPTION
12/16/03	Emails to/from D. Pease asking if we should resend the original IND since it was sent to the incorrect address.
12/15/03	Emails to/from D. Pease regarding where to send the original IND.
12/12/03	Serial #000. Original IND Submission.
12/09/03	Email to D. Pease to identify person to whom cover letter for IND should be addressed.
11/20/03	Received Email of FDA-Generated Telecon Minutes of 11/07/03.
11/07/03	Email to D. Pease: providing list of Savient attendees of teleconference.
11/06/03	Email to D. Pease: teleconference.
11/06/03	Received email from D. Pease re: responses to questions for teleconference.
11/05/03	Email to D. Pease: information for teleconference.
11/04/03	Email to D. Pease: informing her that the meeting will be a teleconference.
11/03/03	Received email from D. Pease re: sponsor's choice for type of meeting.
11/02/03	Email to D. Pease: telecon or face-to-face meeting?
10/29/03	Email to D. Pease: file of letter and protocol.
10/29/03	Letter re: meeting package. Amendment to include draft bioequiv. study protocol.
10/10/03	Email to/from D. Pease: Questions for pre-NDA meeting.
10/09/03	Submission: Pre-NDA Meeting Package.
09/18/03	Received Fax from FDA: pre-NDA Meeting date of November 7, 2003.
09/12/03	Pre-NDA Meeting Request letter.
09/09/03	Email to D. Pease: response to pre-NDA meeting set-up; will be forwarding meeting request letter.
09/09/03	Received Email from D. Pease: response to pre-NDA meeting set-up.
09/09/03	Email to D. Pease: request for information on set-up of pre-NDA meeting.

(B) **NDA Activities**

A list of significant activities undertaken by the marketing applicant in preparation for filing the NDA and during the pendency of NDA 21-807 is provided in Table 2 below:

DATE	DESCRIPTION
11/1/05	Letter to the FDA-Central Document Room regarding the Patent Information Submitted Upon and After Approval of an NDA or Supplement.
10/31/05	Fax received from Christy Cottrell with signed approval letter and labeling for Soltamox™ (tamoxifen citrate) Oral Solution.
10/31/05	Email received from Christy Cottrell with signed approval letter and labeling for Soltamox™ (tamoxifen citrate) Oral Solution.
10/27/05	General Correspondence re: change in contact person; new contact person at Savient is Murad Husain.
10/18/05	Email to FDA (Christy Wilson) re: change in contact information at Savient.
9/28/05	Email to Christy Cottrell re: 9/28/05 email asking about the review status from the Office of Compliance.
9/28/05	Email to FDA re: 9/27/05 FDA Comment on the medication guide.
9/28/95	Received Email from Christy Cottrell re: division obtained "acceptable recommendation" from Office of Compliance.
9/23/05	Email responding to Christy Cottrell's email question regarding submission of the Gail Risk Calculator on a CD; supporting July 21st cover letter is attached.
8/25/05	Email to Cheng Yi Liang, forwarding electronic PDF version of Response to FDA 483 Observation #10 and related questions received via e-mail on August 19, 2005.
8/25/05	Email to Alicia Mozzachio, forwarding an electronic PDF version of the Response to FDA 483 Observation #10 and related questions received via e-mail on August 19, 2005.
8/25/05	Submission to Christy Cottrell – Copy of the Response to FDA 483 Observation #10 and related questions received via e-mail on August 19, 2005.
8/24/05	Email to FDA re: revised draft labeling that was accepted by Savient with additional minor edits.

DATE	DESCRIPTION
8/19/05	Received email from Alicia Mozzachio (Office of Compliance) that included follow-up questions from FDA 483 OBSERVATION # 10.
8/12/05	Submission: Response to the request from the FDA; questions from Dr. Cheng Yi Liang during August 9th telephone conversation regarding storage and exposure of product lot 005380 during the photostability testing and for lot 005769 which was used for simulated in-use stability study.
8/12/05	Fax to Christy Cottrell forwarding copy of submission re: Response to the request from the FDA; questions from Dr. Cheng Yi Liang during August 9th telephone conversation regarding storage and exposure of product lot 005380 during the photostability testing and for lot 005769 which was used for the simulated in-use stability study.
8/5/05	Received Email from FDA re: draft labeling which included FDA revisions.
8/1/05	Email to Christy Cottrell forwarding copy of submission: Response to the request from the FDA; questions from Dr. Cheng Yi Liang during July 29th, 2005 telephone conversation regarding unknown peak observed during analytical method validation.
8/1/05	Fax to Christy Cottrell forwarding copy of submission: Response to the request from the FDA; questions from Dr. Cheng Yi Liang during July 29th, 2005 telephone conversation regarding unknown peak observed during analytical method validation.
8/1/05	Submission: Response to the request from the FDA; questions from Dr. Cheng Yi Liang during July 29th 2005 telephone conversation regarding unknown peak observed during analytical method validation.
7/21/05	Submission: Response to the request from the FDA; submission of Gail Risk Calculator (hand-held low tech) and CDs (high tech).
7/7/05	Email to Christy Cottrell requesting to check with the Reviewers to see whether there are any major issues that we need to address or any documents we can provide to resolve any outstanding issues.
7/5/05	Email to Christy Cottrell re: whether there are more questions Savient needs to address and whether there are any major issues.
6/15/05	Email responding to Christy Cottrell's June 14, 2005 follow-up to CMC questions.
6/15/05	Received Email from FDA requesting status update on the submission of the Gail Risk calculator(s).

DATE	DESCRIPTION
6/14/05	Email from Christy Cottrell re: following up on CMC items from the April 25th Email.
6/7/05	Submission: Response to request from the FDA re: Dosing Cups.
5/31/05	Email to Christy Cottrell stating that dosing cups will be sent as soon as they have been received.
5/31/05	Received Email from FDA requesting sample of the dosing cups
5/18/05	Email responding to Christy Cottrell regarding submission of the high tech and low tech Gail Risk Calculators.
5/18/05	Email from Christy Cottrell requesting Savient to submit high tech and low tech Gail Risk Calculators.
5/6/05	Email to Christy Cottrell informing her that the submission containing the response to the questions from the clinical pharmacology reviewer had been sent out.
5/5/05	Submission: Response to Questions from the Clinical Pharmacology Reviewer was submitted along with the request SAS. Xpt files for both the US study and the European TAMOX 1 study.
5/4/05	Email responding to Christy Cottrell regarding response to the clinical pharmacology questions.
5/4/05	Received Email from Christy Cottrell inquiring if Savient had submitted response to the clinical pharmacology questions.
4/30/05	Submission: Response to CMC Review questions; responding to Christy Cottrell's April 25th Email regarding the questions received from the chemistry reviewer.
4/25/05	Email informing Christy Cottrell that a significant amount of information required to respond to the CMC questions were already included in the application.
4/21/05	Email informing Christy Cottrell that we are in the process of compiling the response and will submit the information by next week. Also Briti received a request from the FDA Field Inspector from PR, Mr. Jose Cruz, wanting to know the name of the reviewing chemist of the NDA 21-807 Soltamox.
4/18/05	Email informing Christy Cottrell that we have received the requested information for the CO501 and C0501-2 studies and are waiting for the information from the TAMOX1 STUDY.

DATE	DESCRIPTION
4/18/05	Received Email from Christy Cottrell, agreeing that Savient could send partial response to the questions from the FDA Clinical Pharmacologist.
4/11/05	Received Email from Christy Cottrell re: request from the Clin Pham reviewer for individual raw PK data in SAS.xpt files from TAMOX1 study and stability study and duration of storage of bioanalytical samples from TAMOX1 and C0501 and C0501-2 studies.
4/11/05	Email to Christy Cottrell re: Questions from the Pharmacology Reviewer.
4/5/05	Meeting with FDA.
4/5/05	Email forwarding to FDA meeting slides for April 5th Meeting in Rockville, MD.
3/24/05	Received Letter from FDA stating determination that NDA is sufficiently completed to permit a substantive review and therefore deemed filed under section 505(b) of the Act on March 13, 2005, in accordance with 21 CFR 314.101(a).
3/23/05	Received Letter from FDA stating that unless Savient is notified within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, the FDA will deem the application filed effective March 13, 2005.
3/22/05	Email forwarding slide presentation to Christy Cottrell for scheduled presentation to FDA on April 5, 2005.
3/11/05	General Correspondence to FDA (Richard Pazdur) re: Desk Copy of Item 6, Human PK Section.
3/11/05	General Correspondence to Christy Cottrell re: Item 6, PK Section sent to Christy Cottrell per her email request on March 9, 2005. Volumes submitted 1.8-1.13.
3/9/05	Telephone Call from Christy Cottrell requesting a Desk Copy of the Human PK section of the NDA as soon as possible.
2/9/05	Received Email from Christy Cottrell confirming the NDA presentation meeting on April 5, 2005.
2/9/05	Email to Christy Cottrell re: FDA meeting on March 14, 2005.
2/9/05	Email responding to Christy Cottrell re: agreement to April 5th date.
2/8/05	Received Email from FDA requests Savient to come to the Division and present the NDA (FDA Meeting).

DATE	DESCRIPTION
2/3/05	Email responding to January 31, 2005 email from Kati Johnson requesting Savient to supply a list of manufacturing sites for the drug substance and drug product, sites of release and stability testing, and packaging sites.
1/31/05	Received Email from FDA chemistry reviewer requesting site information and corresponding addresses and CFN numbers.
1/7/05	General Correspondence re: NDA 21-807, Revised User Fee Form 3397 and Notification of Payment of the User Fee.
1/7/05	Submission: $336,000 User Fee. Submission ID # 4915 (NDA 21-807).
1/04/05	Left voicemail & sent email to Mike Jones, Senior Program Manager, regarding determination of applicability of half user fee for NDA.
1/4/05	Received Notification Letter from FDA stating that FDA has not received user fee for NDA.
1/4/05	Received Email from Christy Cottrell regarding new NDA 21-807 User Fee.
12/27/04	Email to Dorothy Pease forwarding Cover Letter and PDF Copy of NDA 21-807 Original 505(b)(2) Submission.
12/29/04	Submission: Corrections to Original 505(b)(2) submission. Item 3 (Application Summary), Item 8 (Clinical) and Item 10 (Statistics).
12/23/04	Original 505(b)(2) NDA Submission.

12. Statement That the Patent is Eligible for Extension and Statement As to the Length of Extension Claimed (37 CFR 1.740(a)(12))

In the view of the Applicant, the '425 patent is eligible for the requested extension of patent term. The term of the '425 Patent has never been extended under 35 U.S.C. §156(e)(i). The approved product has been subject to a regulatory review by the FDA under the provisions of the Federal Food, Drug and Cosmetic Act before its initial commercial marketing or use. The '425 patent is the only patent to be extended for the regulatory review period for SOLTAMOX™ tamoxifen oral solution. This application for extension of patent term has been duly made by the owner of record (through an assignment from Akzo Nobel N.V. recorded at Reel 014336/Frame 0509) of the '425 patent in accordance with the requirements of 35 U.S.C. §156(d)(1)-(4).

In the opinion of the Applicant, the '425 patent is entitled to an extension of 481 days (i.e., resulting in an extended expiry date of October 20, 2019). The extension of 481 days was calculated by the method described in 37 CFR § 1.775.

The number of days by which the '425 patent should be extended was calculated as follows:

(A) Length of Regulatory Review Period (37 CFR 1.775(c))

The number of days for the testing phase as defined in 37 CFR § 1.775(c)(1) (i.e., the number of days from the effective date of the IND, January 16, 2004, until the NDA submission date, December 23, 2004) is **342 days**.

The number of days for the approval phase as defined in 37 CFR § 1.775(c)(2) (i.e., the number of days from the NDA submission date, December 23, 2004, until the NDA approval date, October 29, 2005) is **310 days**.

The length of the regulatory review period is the sum of the number of days calculated pursuant to 37 C.F.R. § 1.775(c)(1) and the number of days calculated pursuant to 37 C.F.R. § 1.775(c)(2): **652 days**.

(B) Calculations Pursuant to 37 CFR § 1.775(d)(1)

The patent issued on October 3, 2000, and the regulatory review period began on January 16, 2004. Hence, the number of days in the regulatory review period (as defined in 37 C.F.R. § 1.775(c)) that were on or before the date on which the patent issued is **0 days**.

The number of days in the periods of paragraphs (c)(1) and (c)(2) of 37 C.F.R. § 1.775 during which it is determined under 35 U.S.C. § 156(d)(2)(B) by the Secretary of Health and Human Services that Applicant did not act with due diligence is **0 days**.

One-half the number of days in the period defined in paragraph (c)(1) of 37 C.F.R. § 1.775 (reduced in accordance with paragraphs (d)(1)(i) and (d)(1)(ii)) is **171 days**.

Therefore, the maximum patent term extension allowed under 37 C.F.R. § 1.775(d)(1) is 652 minus 171 – or **481 days**.

(C) Calculations Pursuant to 37 CFR § 1.775(d)(2)

The extended expiry date calculated pursuant to 37 C.F.R. § 1.775(d)(2) is **October 20, 2019**, which is calculated by adding 481 days to the original term of the patent as shortened by any terminal disclaimer.

(D) Calculations Pursuant to 37 CFR § 1.775(d)(3)

The extended expiry date calculated pursuant to 37 C.F.R. § 1.775(d)(3) is **October 29, 2019**, which is calculated by adding 14 years to the NDA approval date of October 29, 2005.

(E) Calculations Pursuant to 37 CFR § 1.775(d)(4)

The extended expiry date pursuant to 37 C.F.R. § 1.775(d)(4) is determined by selecting the earlier of the dates obtained pursuant to paragraphs (d)(2) and (d)(3) of 37 C.F.R. § 1.775: **October 20, 2019**.

(F) Calculations Pursuant to 37 CFR § 1.775(d)(5)

The extended expiry date calculated pursuant to 37 C.F.R. § 1.775(d)(5)(i) is **June 26, 2023**, which is calculated by adding five (5) years to the original expiry date as shortened by any terminal disclaimer. The extended expiry date pursuant to 37 C.F.R. § 1.775(d)(5)(ii) is determined by selecting the earlier of the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of 37 C.F.R. § 1.775: **October 20, 2019**.

(F) Calculations Pursuant to 37 CFR § 1.775(d)(6)

37 C.F.R. § 1.775(d)(6) does not apply because the '425 patent issued after September 24, 1984. Hence, no adjustment was made.

Therefore, the '425 patent is entitled to an extension of **481 days**, thereby resulting in an extended expiry date of **October 20, 2019**.

13. Statement That Applicant Acknowledges Duty to Disclose to the Director of the USPTO and the Secretary of Health and Human Services Any Information Which is Material to the Determination of Entitlement to the Extension Sought (37 CFR 1.740(a)(13))

Savient acknowledges the duty to disclose to the Director of the United States and Trademark Office and the Secretary of Health and Human Services any information which is

material to the determination of entitlement to the extension sought in accordance with the provisions of 37 C.F.R. 1.765.

14. Prescribed Fee (37 CFR 1.740(a)(14))

The fee prescribed in 37 CFR 1.20(j)(1) is attached hereto in the form of a check in the amount of $1,120. Applicant hereby authorizes the Director to charge of any fee deficiency or credit any overpayment to Deposit Account No. 50-0832.

15. Correspondence Information (37 CFR 1.740(a)(15))

Please address all correspondence and other communications regarding this request for extension to Customer No. 49,432, which corresponds to:

Peter Tu, Esq.
Associate General Counsel & Senior Director, Intellectual Property
Savient Pharmaceuticals, Inc.
One Tower Center, 14th Floor
East Brunswick, New Jersey 08816
Tel: (732) 565-4744
Fax: (732) 418-3687
E-mail: ptu@savientpharma.com

16. Power of Attorney (37 CFR 1.730(b)(2) & (d))

Applicant is the assignee of record of the entire right, title and interest in U.S. Patent No. 6,127,425 (the '425 patent). Enclosed are: (i) an executed Statement Under 37 CFR 3.73(b) (attached as Exhibit D) and an executed power of attorney appointing the undersigned as the agent/attorney for Applicant (attached as Exhibit E).

In view of the foregoing, Applicant submits that the '425 patent is entitled to the requested extension of patent term, and early notification of such action is earnestly solicited.

Respectfully submitted,

SAVIENT PHARMACEUTICALS, INC.

Peter Tu

Peter Tu
Registration No. 43,207

Savient Pharmaceuticals, Inc.
One Tower Center
East Brunswick, NJ 08816
Tel: (732) 565-4744
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E-mail: ptu@savientpharma.com

A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-807

Savient Pharmaceuticals, Inc.
One Tower Center Blvd., 14th floor
East Brunswick, NJ 08816

Attention: Murad Husain
Vice President, Regulatory Affairs

Dear Mr. Husain:

Please refer to your new drug application (NDA) dated December 23, 2004, received January 12, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Soltamox™ (tamoxifen citrate) Oral Solution 10mg/5mL.

We acknowledge receipt of your submissions dated December 29, 2004, January 7, February 3, April 30, May 5, June 7 and 15, July 21, and August 1, 12, and 25, 2005.

This new drug application provides for the use of Soltamox™ (tamoxifen citrate) Oral Solution for the following indications:

- **Metastatic Breast Cancer:** Tamoxifen citrate is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, tamoxifen citrate is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from tamoxifen citrate therapy.

- **Adjuvant Treatment of Breast Cancer:** Tamoxifen citrate is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. In some tamoxifen citrate adjuvant studies, most of the benefit to date has been in the subgroup with four or more positive axillary nodes.

  Tamoxifen citrate is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.

  The estrogen and progesterone receptor values may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial.

  Tamoxifen citrate reduces the occurrence of contralateral breast cancer in patients receiving adjuvant tamoxifen citrate therapy for breast cancer.

- **Ductal Carcinoma in Situ (DCIS):** In women with DCIS, following breast surgery and radiation, tamoxifen citrate is indicated to reduce the risk of invasive breast cancer (see **BOXED WARNING** at the beginning of the label). The decision regarding therapy with tamoxifen for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen therapy.

  Current data from clinical trials support five years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

- **Reduction in Breast Cancer Incidence in High Risk Women:** Tamoxifen citrate is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. This effect was shown in a study of 5 years planned duration with a median follow-up of 4.2 years. Twenty-five percent of the participants received drug for 5 years. The longer term effects are not known. In this study, there was no impact of tamoxifen on overall or breast cancer-related mortality (see **BOXED WARNING** at the beginning of the label).

  Tamoxifen citrate is indicated only for high-risk women. "High risk" is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer $\geq$ 1.67%, as calculated by the Gail Model.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide, immediate container and carton labels) and must also include the Gail Model Risk Assessment Tools (CD-ROM and calculator) as submitted on July 21, 2005. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-807**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 796-1347.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

SOLTAMOX™ Oral Solution
Rx Only

WARNING - For Women with Ductal Carcinoma in Situ (DCIS) and Women at High Risk for Breast Cancer: *Serious and life-threatening events associated with tamoxifen in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism. Incidence rates for these events were estimated from the NSABP P-1 trial (see* ***CLINICAL PHARMACOLOGY, Clinical Studies, Reduction in Breast Cancer Incidence In High Risk Women).***

*Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1,000 women-years of 2.20 for tamoxifen vs. 0.71 for placebo) and uterine sarcoma (incidence rate per 1,000 women years of 0.17 for tamoxifen vs. 0.0 for placebo) *. For stroke, the incidence rate per 1,000 women years was 1.43 for tamoxifen vs. 1.00 for placebo**. For pulmonary embolism, the incidence rate per 1,000 women years was 0.75 for tamoxifen versus 0.25 for placebo * *.*

Some of the strokes, pulmonary emboli, and uterine malignancies were fatal.

Health care providers should discuss the potential benefits versus the potential risks of these serious events with women at high risk of breast cancer and women with DCIS considering tamoxifen to reduce their risk of developing breast cancer.

The benefits of tamoxifen outweigh its risks in women already diagnosed with breast cancer.

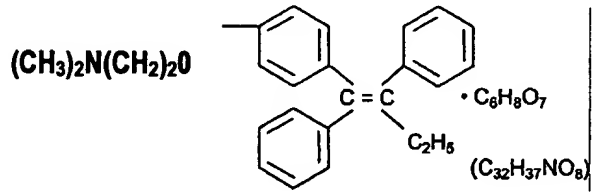
* *Updated long-term follow-up data (median length of follow-up is 6.9 years) from NSABP P-1 study. See* ***WARNINGS, Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma.***

** *See Table 3 under* ***CLINICAL PHARMACOLOGY, Clinical Studies.***

DESCRIPTION

SOLTAMOX™ solution, a nonsteroidal antiestrogen, is for oral administration. Each 5 mL solution contains 15.2 mg tamoxifen citrate, equivalent to 10 mg tamoxifen and the following inactive ingredients: ethanol, glycerol, propylene glycol, sorbitol solution, licorice flavor, aniseed flavor, purified water.

The chemical name is (Z)2-[4-(1,2-diphenyl-l-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3- propanetricarboxylate (1:1). The structural and empirical formulas are:



Tamoxifen citrate has a molecular weight of 563.62, the pKa' is 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/mL and in 0.02 N HCl at 37°C, it is 0.2 mg/mL.

CLINICAL PHARMACOLOGY

Tamoxifen citrate is a nonsteroidal agent that has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to exert its antitumor effects by binding the estrogen receptors.
In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein.

Absorption and Bioavailability

A pharmacokinetic study was performed in healthy perimenopausal and postmenopausal female subjects to evaluate the bioavailability of SOLTAMOX™(n=30) in comparison with the commercially available tamoxifen citrate tablets (n=33) under fasting conditions. A third arm evaluated the effect of food on SOLTAMOX™ (n=16 evaluable). The rate and extent of absorption of SOLTAMOX™ was found to be bioequivalent to that of tamoxifen citrate tablets under fasting conditions.

In the food effect arm, the C_{max} and AUC were comparable to the fasting group. T_{max} was slightly longer in the fed group. There was no difference in bioavailability of SOLTAMOX™ Oral Solution between fed and fasting states, and therefore SOLTAMOX™ can be given without regard to meals.

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 mg/mL (range 35 to 45 ng/mL) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/mL (range 10 to 20 ng/mL). Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/mL (range 67-183 ng/mL) for tamoxifen and 336 ng/mL (range 148-654 ng/mL) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 ng/mL (range 71-183 ng/mL) and 353 ng/mL (range 152-706 ng/mL), respectively. After initiation of therapy, steady-state concentrations for tamoxifen are achieved in about 4 weeks and steady-state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady-state, crossover study of 10 mg tamoxifen tablets given twice a day vs. a 20 mg tamoxifen tablet given once daily, the 20 mg tamoxifen tablet was bioequivalent to the 10 mg tamoxifen tablets.

Metabolism

Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

Excretion
Studies in women receiving 20 mg of ^{14}C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

Special Populations
The effects of age, gender and race on the pharmacokinetics of tamoxifen have not been determined. The effects of reduced liver function on the metabolism and pharmacokinetics of tamoxifen have not been determined.

Pediatric Patients
The use of SOLTAMOX™ in pediatric patients has not been evaluated.

Drug-drug Interactions
In vitro studies showed that erythromycin, cyclosporine, nifedipine and diltiazem competitively inhibited formation of N-desmethyl tamoxifen with apparent K_I of 20, 1, 45 and 30 μM, respectively. The clinical significance of these *in vitro* studies is unknown.

Tamoxifen reduced the plasma concentration of letrozole by 37% when these drugs were co-administered. Rifampin, a cytochrome P-450 3A4 inducer reduced tamoxifen AUC and C_{max} by 86% and 55%, respectively. Aminoglutethimide reduces tamoxifen and N-desmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

Clinical Studies

Metastatic Breast Cancer:
Premenopausal Women (Tamoxifen Citrate vs. Ablation) - Three prospective, randomized studies (Ingle, Pritchard, Buchanan) compared tamoxifen to ovarian ablation (oophorectomy or ovarian irradiation) in premenopausal women with advanced breast cancer. Although the objective response rate, time to treatment failure, and survival were similar with both treatments, the limited patient accrual prevented a demonstration of equivalence. In an overview analysis of survival data from the 3 studies, the hazard ratio for death (tamoxifen /ovarian ablation) was 1.00 with two-sided 95% confidence intervals of 0.73 to 1.37. Elevated serum and plasma estrogens have been observed in premenopausal women receiving tamoxifen, but the data from the randomized studies do not suggest an adverse effect of this increase. A limited number of premenopausal patients with disease progression during tamoxifen therapy responded to subsequent ovarian ablation.

Male Breast Cancer:
Published results from 122 patients (119 evaluable) and case reports in 16 patients (13 evaluable) treated with tamoxifen have shown that tamoxifen is effective for the palliative treatment of male breast cancer. Sixty-six of these 132 evaluable patients responded to tamoxifen which constitutes a 50% objective response rate.

Adjuvant Breast Cancer:
Overview
The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, and again in

1995. In 1998, 10-year outcome data were reported for 36,689 women in 55 randomized trials of adjuvant tamoxifen using doses of 20-40 mg/day for 1-5+ years. Twenty-five percent of patients received 1 year or less of trial treatment, 52% received 2 years, and 23% received about 5 years. Forty-eight percent of tumors were estrogen receptor (ER) positive (> 10 fmol/mg), 21% were ER poor (< 10 fmol/l), and 31% were ER unknown. Among 29,441 patients with ER positive or unknown breast cancer, 58% were entered into trials comparing tamoxifen to no adjuvant therapy and 42% were entered into trials comparing tamoxifen in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node positive disease and 46% had node negative disease.
Among women with ER positive or unknown breast cancer and positive nodes who received about 5 years of treatment, overall survival at 10 years was 61.4% for tamoxifen vs. 50.5% for control (logrank $2p < 0.00001$). The recurrence-free rate at 10 years was 59.7% for tamoxifen vs. 44.5% for control (logrank $2p < 0.00001$). Among women with ER positive or unknown breast cancer and negative nodes who received about 5 years of treatment, overall survival at 10 years was 78.9% for tamoxifen vs. 73.3% for control (logrank $2p < 0.00001$). The recurrence-free rate at 10 years was 79.2% for tamoxifen versus 64.3% for control (logrank $2p < 0.00001$).

The effect of the scheduled duration of tamoxifen may be described as follows. In women with ER positive or unknown breast cancer receiving 1 year or less, 2 years or about 5 years of tamoxifen, the proportional reductions in mortality were 12%, 17% and 26%, respectively (trend significant at $2p < 0.003$). The corresponding reductions in breast cancer recurrence were 21%, 29% and 47% (trend significant at $2p < 0.00001$).

Benefit is less clear for women with ER poor breast cancer in whom the proportional reduction in recurrence was 10% ($2p = 0.007$) for all durations taken together, or 9% ($2p = 0.02$) if contralateral breast cancers are excluded. The corresponding reduction in mortality was 6% (NS). The effects of about 5 years of tamoxifen on recurrence and mortality were similar regardless of age and concurrent chemotherapy. There was no indication that doses greater than 20 mg per day were more effective.

Node Positive - Individual Studies:
Two studies (Hubay and NSABP B-09) demonstrated an improved disease-free survival following radical or modified radical mastectomy in postmenopausal women or women 50 years of age or older with surgically curable breast cancer with positive axillary nodes when tamoxifen was added to adjuvant cytotoxic chemotherapy. In the Hubay study, tamoxifen was added to "low-dose" CMF (cyclophosphamide, methotrexate and fluorouracil). In the NSABP B-09 study, tamoxifen was added to melphalan [L-phenylalanine mustard (P)] and fluorouracil (F).

In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50-59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while there was a nonstatistically significant trend toward adverse effect in women with both estrogen and progesterone receptor levels less than 10 fmol. In women age 60-70 years, there was a trend toward a beneficial effect of tamoxifen without any clear relationship to estrogen or progesterone receptor status.

Three prospective studies (ECOG-1178, Toronto, NATO) using tamoxifen adjuvantly as a single agent demonstrated an improved disease-free survival following total mastectomy and axillary dissection for postmenopausal women with positive axillary nodes compared

to placebo/no treatment controls. The NATO study also demonstrated an overall survival benefit.

Node Negative - Individual Studies:
NSABP B-14, a prospective, double-blind, randomized study, compared tamoxifen to placebo in women with axillary node-negative, estrogen-receptor positive (≥10 fmol/mg cytosol protein) breast cancer (as adjuvant therapy, following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). After five years of treatment, there was a significant improvement in disease-free survival in women receiving tamoxifen. This benefit was apparent both in women under age 50 and in women at or beyond age 50.

One additional randomized study (NATO) demonstrated improved disease-free survival for tamoxifen compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of tamoxifen appeared to be independent of estrogen receptor status.

Duration of Therapy:
In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy.

In the NSABP B-14 trial, in which patients were randomized to tamoxifen 20 mg/day for 5 years vs. placebo and were disease-free at the end of this 5-year period were offered rerandomization to an additional 5 years of tamoxifen or placebo. With 4 years of follow-up after this rerandomization, 92% of the women that received 5 years of tamoxifen were alive and disease-free, compared to 86% of the women scheduled to receive 10 years of tamoxifen (p=0.003). Overall survivals were 96% and 94%, respectively (p=0.08). Results of the B-14 study suggest that continuation of therapy beyond 5 years does not provide additional benefit.

A Scottish trial of 5 years of tamoxifen vs. indefinite treatment found a disease-free survival of 70% in the five-year group and 61% in the indefinite group, with 6.2 years median follow-up (HR= 1.27, 95% CI: 0.87-1.85).

In a large randomized trial conducted by the Swedish Breast Cancer Cooperative Group of adjuvant tamoxifen 40 mg/day for 2 or 5 years, overall survival at 10 years was estimated to be 80% in the patients in the 5-year tamoxifen group, compared with 74% among corresponding patients in the 2-year treatment group (p=0.03). Disease-free survival at 10 years was 73% in the 5-year group and 67% in the 2-year group (p=0.009). Compared with 2 years of tamoxifen treatment, 5 years of treatment resulted in a slightly greater reduction in the incidence of contralateral breast cancer at 10 years, but this difference was not statistically significant.

Contralateral Breast Cancer:
The incidence of contralateral breast cancer is reduced in breast cancer patients (premenopausal and postmenopausal) receiving tamoxifen compared to placebo. Data on contralateral breast cancer are available from 32,422 out of 36,689 patients in the 1995 overview analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG). In clinical trials with tamoxifen of 1 year or less, 2 years, and about 5 years duration, the proportional reductions in the incidence rate of contralateral breast cancer among women

receiving tamoxifen were 13% (NS), 26% (2p = 0.004) and 47% (2p < 0.00001), with a significant trend favoring longer tamoxifen duration (2p = 0.008). The proportional reductions in the incidence of contralateral breast cancer were independent of age and ER status of the primary tumor. Treatment with about 5 years of tamoxifen reduced the annual incidence rate of contralateral breast cancer from 7.6 per 1,000 patients in the control group compared with 3.9 per 1,000 patients in the tamoxifen group.

In a large randomized trial in Sweden (the Stockholm Trial) of adjuvant tamoxifen 40 mg/day for 2-5 years, the incidence of second primary breast tumors was reduced 40% (p < 0.008) on tamoxifen compared to control. In the NSABP B-14 trial in which patients were randomized to tamoxifen 20 mg/day for 5 years vs. placebo, the incidence of second primary breast cancers was also significantly reduced (p < 0.01). In NSABP B-14, the annual rate of contralateral breast cancer was 8.0 per 1,000 patients in the placebo group compared with 5.0 per 1,000 patients in the tamoxifen group, at 10 years after first randomization.

Ductal Carcinoma in Situ:
NSABP B-24, a double-blind, randomized trial included women with ductal carcinoma in situ (DCIS). This trial compared the addition of tamoxifen or placebo to treatment with lumpectomy and radiation therapy for women with DCIS. The primary objective was to determine whether 5 years of tamoxifen therapy (20 mg/day) would reduce the incidence of invasive breast cancer in the ipsilateral (the same) or contralateral (the opposite) breast.

In this trial 1,804 women were randomized to receive either tamoxifen or placebo for 5 years: 902 women were randomized to tamoxifen 10 mg tablets twice a day and 902 women were randomized to placebo. As of December 31, 1998, follow-up data were available for 1,798 women and the median duration of follow-up was 74 months.

The tamoxifen and placebo groups were well balanced for baseline demographic and prognostic factors. Over 80% of the tumors were less than or equal to 1 cm in their maximum dimension, were not palpable, and were detected by mammography alone. Over 60% of the study population was postmenopausal. In 16% of patients, the margin of the resected specimen was reported as being positive after surgery. Approximately half of the tumors were reported to contain comedo necrosis.

For the primary endpoint, the incidence of invasive breast cancer was reduced by 43% among women assigned to tamoxifen (44 cases - tamoxifen, 74 cases - placebo; p=0.004; relative risk (RR)=0.57, 95% CI: 0.39-0.84). No data are available regarding the ER status of the invasive cancers. The stage distribution of the invasive cancers at diagnosis was similar to that reported annually in the SEER data base.

Results are shown in Table 1. For each endpoint the following results are presented: the number of events and rate per 1,000 women per year for the placebo and tamoxifen groups; and the relative risk (RR) and its associated 95% confidence interval (CI) between tamoxifen and placebo. Relative risks less than 1.0 indicate a benefit of tamoxifen therapy. The limits of the confidence intervals can be used to assess the statistical significance of the benefits of tamoxifen therapy. If the upper limit of the CI is less than 1.0, then a statistically significant benefit exists.

Table 1
Major Outcomes of the NSABP B-24 Trial

Type of Event	Lumpectomy, radiotherapy, and placebo		Lumpectomy, radiotherapy, and tamoxifen		RR	95% CI Limits
	No. of events	Rate per 1000 women per year	No. of events	Rate per 1000 women per year		
Invasive breast cancer (Primary endpoint)	**74**	**16.73**	**44**	**9.60**	**0.57**	**0.39 to 0.84**
-Ipsilateral	47	10.61	27	5.90	0.56	0.33 to 0.91
-Contralateral	25	5.64	17	3.71	0.66	0.33 to 1.27
-Side undetermined	2	-	0	-	-	
Secondary Endpoints						
DCIS	56	12.66	41	8.95	0.71	0.46 to 1.08
-Ipsilateral	46	10.40	38	8.29	0.88	0.51 to 1.25
-Contralateral	10	2.26	3	0.65	0.29	0.05 to 1.13
All Breast Cancer Events	129	29.16	84	18.34	0.63	0.47 to 0.83
-All Ipsilateral events	96	21.70	65	14.19	0.65	0.47 to 0.91
-All Contralateral events	37	8.36	20	4.37	0.52	0.29 to 0.92
Deaths	32		28			
Uterine Malignancies[1]	4		9			
Endometrial Adenocarcinoma[1]	4	0.57	8	1.15		
Uterine Sarcoma[1]	0	0.0	1	0.14		
Secondary primary malignancies (other than endometrial and breast)	30		29			
Stroke	2		7			
Thromboembolic events (DVT, PE)	5		15			

[1]Updated follow-up data (median 8.1 years)

Survival was similar in the placebo and tamoxifen groups. At 5 years from study entry, survival was 97% for both groups.

Reduction in Breast Cancer Incidence in High Risk Women:
The Breast Cancer Prevention Trial (BCPT, NSABP P-1) was a double-blind, randomized, placebo-controlled trial with a primary objective to determine whether 5 years of tamoxifen therapy (20 mg/day) would reduce the incidence of invasive breast cancer in women at high risk for the disease (See **INDICATIONS AND USAGE**). Secondary objectives included an evaluation of the incidence of ischemic heart disease; the effects on the incidence of bone fractures; and other events that might be associated with the use of tamoxifen, including: endometrial cancer, pulmonary embolus, deep vein thrombosis, stroke, and cataract formation and surgery (See **WARNINGS**).

The Gail Model was used to calculate predicted breast cancer risk for women who were less than 60 years of age and did not have lobular carcinoma in situ (LCIS). The following risk factors were used: age; number of first-degree female relatives with breast cancer; previous breast biopsies; presence or absence of atypical hyperplasia; nulliparity; age at first live birth; and age at menarche. A 5-year predicted risk of breast cancer of $\geq$ 1.67% was required for entry into the trial.

In this trial, 13,388 women of at least 35 years of age were randomized to receive either tamoxifen or placebo for five years. The median duration of treatment was 3.5 years. As

of January 31, 1998, follow-up data is available for 13,114 women. Twenty-seven percent of women randomized to placebo (1,782) and 24% of women randomized to tamoxifen (1,596) completed 5 years of therapy. The demographic characteristics of women on the trial with follow-up data are shown in Table 2.

Table 2
Demographic Characteristics of Women in the NSABP P-1 Trial

Characteristic	Placebo		Tamoxifen	
	#	%	#	%
Age (yrs.)				
35-39	184	3	158	2
40-49	2,394	36	2,411	37
50-59	2,011	31	2,019	31
60-69	1,588	24	1,563	24
≥70	393	6	393	6
Age at first live birth (yrs.)				
Nulliparous	1,202	18	1,205	18
12-19	915	14	946	15
20-24	2,448	37	2,449	37
25-29	1,399	21	1,367	21
≥30	606	9	577	9
Race				
White	6,333	96	6,323	96
Black	109	2	103	2
Other	128	2	118	2
Age at menarche				
≥14	1,243	19	1,170	18
12-13	3,610	55	3,610	55
≤11	1,717	26	1,764	27
# of first degree relatives with breast cancer				
0	1,584	24	1,525	23
1	3.714	57	3,744	57
2+	1,272	19	1,275	20
Prior Hysterectomy				
No	4,173	63.5	4,018	62.4
Yes	2,397	36.5	2,464	37.7
# of previous breast biopsies				
0	2,935	45	2,923	45
1	1,833	28	1,850	28
≥2	1,802	27	1,771	27
History of atypical hyperplasia in the breast				
No	5,958	91	5,969	91
Yes	612	9	575	9
History of LCIS at entry				
No	6,165	94	6,135	94
Yes	405	6	409	6
5-year predicted breast cancer risk (%)				
≤2.00	1,646	25	1,626	25
2.01-3.00	2,028	31	2,057	31
3.01-5.00	1,787	27	1,707	26
≥5.01	1,109	17	1,162	18
Total	6,570	100.0	6,544	100.0

Results are shown in Table 3. After a median follow-up of 4.2 years, the incidence of invasive breast cancer was reduced by 44% among women assigned to tamoxifen (86 cases-tamoxifen, 156 cases-placebo; $p<0.00001$; relative risk (RR)=0.56, 95% CI: 0.43-0.72). A reduction in the incidence of breast cancer was seen in each prospectively specified age group (≤ 49, 50-59, ≥ 60), in women with or without LCIS, and in each of the absolute risk levels specified in Table 3. A non-significant decrease in the incidence of ductal carcinoma in situ (DCIS) was seen (23-tamoxifen, 35-placebo; RR=0.66; 95% CI: 0.39-1.11).

There was no statistically significant difference in the number of myocardial infarctions, severe angina, or acute ischemic cardiac events between the two groups (61-tamoxifen, 59-placebo; RR=1.04, 95% CI: 0.73-1.49).

No overall difference in mortality (53 deaths in tamoxifen group vs. 65 deaths in placebo group) was present. No difference in breast cancer-related mortality was observed (4 deaths in tamoxifen group vs. 5 deaths in placebo group).

Although there was a non-significant reduction in the number of hip fractures (9 on tamoxifen, 20 on placebo) in the tamoxifen group, the number of wrist fractures was similar in the two treatment groups (69 on tamoxifen, 74 on placebo). No information regarding bone mineral density or other markers of osteoporosis is available.

The risks of tamoxifen therapy include endometrial cancer, DVT, PE, stroke, cataract formation and cataract surgery (See **Table 3**). In the NSABP P-1 trial, 33 cases of endometrial cancer were observed in the tamoxifen group vs. 14 in the placebo group (RR=2.48, 95% CI: 1.27-4.92). Deep vein thrombosis was observed in 30 women receiving tamoxifen vs. 19 in women receiving placebo (RR=1.59, 95% CI: 0.86-2.98). Eighteen cases of pulmonary embolism were observed in the tamoxifen group vs. 6 in the placebo group (RR=3.01, 95% CI: 1.15-9.27). There were 34 strokes on the tamoxifen arm and 24 on the placebo arm (RR=1.42; 95% CI 0.82-2.51). Cataract formation in women without cataracts at baseline was observed in 540 women taking tamoxifen vs. 483 women receiving placebo (RR=1.13, 95% CI: 1.00-1.28). Cataract surgery (with or without cataracts at baseline) was performed in 201 women taking tamoxifen vs. 129 women receiving placebo (RR=1.51, 95% CI 1.21-1.89) (See **WARNINGS**).

Table 3 summarizes the major outcomes of the NSABP P-1 trial. For each endpoint, the following results are presented: the number of events and rate per 1,000 women per year for the placebo and tamoxifen groups; and the relative risk (RR) and its associated 95% confidence interval (CI) between tamoxifen and placebo. Relative risks less than 1.0 indicate a benefit of tamoxifen therapy. The limits of the confidence intervals can be used to assess the statistical significance of the benefits or risks of tamoxifen therapy. If the upper limit of the CI is less than 1.0, then a statistically significant benefit exists.
For most participants, multiple risk factors would have been required for eligibility. This table considers risk factors individually, regardless of other co-existing risk factors, for women who developed breast cancer. The 5-year predicted absolute breast cancer risk accounts for multiple risk factors in an individual and should provide the best estimate of individual benefit (See **INDICATIONS AND USAGE**).

Table 3
Major Outcomes of the NSABP-1 Trial

	# of Events		Rate/1000 Women/Year			
Type of Event	**Placebo**	**Tamoxifen**	**Placebo**	**Tamoxifen**	**RR**	**95% CI Limits**
Invasive Breast Cancer	156	86	6.49	3.58	0.56	0.43-0.72
Age ≤49	59	38	6.34	4.11	0.65	0.43-0.98
Age 50-59	46	25	6.31	3.53	0.56	0.35-0.91
Age ≥60	51	23	7.17	3.22	0.45	0.27-0.74
Risk Factors for Breast Cancer History, LCIS						
No	140	78	6.23	3.51	0.56	0.43-0.74
Yes	16	8	12.73	6.33	0.50	0.21-1.17
History, Atypical Hyperplasia						
No	138	84	6.37	3.89	0.61	0.47-0.80
Yes	18	2	8.69	1.05	0.12	0.03-0.52
No. First Degree Relatives						
0	32	17	5.97	3.26	0.55	0.30-0.98
1	80	45	5.81	3.31	0.57	0.40-0.82
2	35	18	8.92	4.67	0.52	0.30-0.92
≥3	9	6	13.33	7.58	0.57	0.20-1.59
5-Year Predicted Breast Cancer (as calculated by the Gail Model)						
≤2.00%	31	13	5.36	2.26	0.42	0.22-0.81
2.01-3.00%	39	28	5.25	3.83	0.73	0.45-1.18
3.01-5.00%	36	26	5.37	4.06	0.76	0.46-1.26
≥5.00%	50	19	13.15	4.71	0.36	0.21-0.61
DCIS	35	23	1.47	0.97	0.66	0.39-1.11
Fractures (protocol-specified sites)	92[1]	76[1]	3.87	3.20	0.61	0.83-1.12
Hip	20	9	0.84	0.38	0.45	0.18-1.04
Wrist[2]	74	69	3.11	2.91	0.93	0.67-1.29
Totalischemic Events	59	61	2.47	2.57	1.04	0.71-1.51
Myocardial Infarction	27	27	1.13	1.13	1.00	0.57-1.78
Fatal	8	7	0.33	0.29	0.88	0.27-2.77
Nonfatal	19	20	0.79	0.84	1.06	0.54-2.09
Angina3	12	12	0.50	0.50	1.00	0.41-2.44
Acute Ischemic Syndrome4	20	22	0.84	0.92	1.11	0.58-2.13
Uterine						
Malignancies (among women with an intact uterus)[10]	17	57				
Endometrial	17	53	0.71	2.20		
Adenocarcinoma[10]	0	4	0.0	0.17		
Uterine Sarcoma[10]						
Stroke[5]	24	34	1.00	1.43	1.42	0.82-2.51
Transient Ischemic Attack	21	18	0.88	0.75	0.86	0.43-1.70
Pulmonary Emboli[6]	6	18	0.25	0.75	3.01	1.15-9.27
Deep-Vein Thrombosis[6]	19	30	0.79	1.26	1.59	0.86-2.98
Cataracts Developing on Study[9]	483	540	22.51	25.41	1.13	1.00-1.28
Underwent Cataract Surgery[8]	63	101	2.83	4.57	1.62	1.18-2.22
Underwent Cataract Surgery[9]	1.29	201	5.44	8.56	1.58	1.26-1.97

1 Two women had hip and wrist fractures
2 Includes Colles' and other lower radius fractures
3 Requiring angioplasty or CABG
4 New Q-wave on ECG; no angina or elevation of serum enzymes; or angina requiring hospitalization without surgery
5 Seven cases were fatal; three in the placebo group and four in the tamoxifen citrate group
6 Three cases in the tamoxifen citrate group were fatal
7 All but three cases in each group required hospitalization
8 Based on women without cataracts at baseline (6,230-Placebo, 6,199-tamoxifen citrate)
9 All women (6,707-placebo, 6,681-tamoxifen citrate)
10 Updated long-term follow-up data, (median 6.9 years) from NSABP P-1 study added after cut-off for the other information in this table.

Table 4 describes the characteristics of the breast cancers in the NSABP P-1 trial and includes tumor size, nodal status, ER status. Tamoxifen citrate decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors.

Table 4
Characteristics of Breast Cancer in NSABP P-1 Trial

Staging Parameter	Placebo N=156	Tamoxifen N=86	Total N=242
Tumor size			
T1	117	60	177
T2	28	20	48
T3	7	3	10
T4	1	2	3
Unknown	3	1	4
Nodal status			
Negative	103	56	159
1-3 positive nodes	29	14	43
≤4 positive nodes	10	12	22
Unknown	14	4	18
Stage			
I	88	47	135
II: node negative	15	9	24
II: node positive	33	22	55
III	6	4	10
IV	21	1	3
Unknown	12	3	15
Estrogen receptor			
Positive	115	38	153
Negative	27	36	63
Unknown	14	12	26

[1] One participant presented with a suspicious bone scan but did not have documented metastases. She subsequently died of metastatic breast cancer.

Interim results from 2 trials in addition to the NSABP P-1 trial examining the effects of tamoxifen in reducing breast cancer incidence have been reported.

The first was the Italian Tamoxifen Prevention trial. In this trial women between the ages of 35 and 70, who had had a total hysterectomy, were randomized to receive 20 mg tamoxifen or matching placebo for 5 years. The primary endpoints were occurrence of, and death from, invasive breast cancer. Women without any specific risk factors for breast cancer were to be entered. Between 1992 and 1997, 5,408 women were randomized. Hormone Replacement Therapy (HRT) was used in 14% of participants. The trial closed in 1997 due to the large number of dropouts during the first year of treatment (26%). After 46 months of follow-up there were 22 breast cancers in women on placebo and 19 in women on tamoxifen. Although no decrease in breast cancer incidence was observed, there was a trend for a reduction in breast cancer among women receiving protocol therapy for at least 1 year (19-placebo, 11-tamoxifen). The small numbers of participants along with the low level of risk in this otherwise healthy group precluded an adequate assessment of the effect of tamoxifen in reducing the incidence of breast cancer.

The second trial, the Royal Marsden Trial (RMT) was reported as an interim analysis. The RMT was begun in 1986 as a feasibility study of whether larger scale trials could be mounted. The trial was subsequently extended to a pilot trial to accrue additional participants to further assess the safety of tamoxifen. Twenty-four hundred and seventy-one women were entered between 1986 and 1996; they were selected on the basis of a family history of breast cancer. HRT was used in 40% of participants. In this trial, with a 70-month median follow-up, 34 and 36 breast cancers (8 noninvasive, 4 on each arm) were observed among women on tamoxifen and placebo, respectively. Patients in this trial were younger than those in the NSABP P-1 trial and may have been more likely to develop ER (-) tumors, which are unlikely to be reduced in number by tamoxifen therapy. Although women were selected on the basis of family history and were thought to have a high risk of breast cancer, few events occurred, reducing the statistical power of the study. These factors are potential reasons why

the RMT may not have provided an adequate assessment of the effectiveness of tamoxifen in reducing the incidence of breast cancer.

In these trials, an increased number of cases of deep vein thrombosis, pulmonary embolus, stroke, and endometrial cancer were observed on the tamoxifen arm compared to the placebo arm. The frequency of events was consistent with the safety data observed in the NSABP P-1 trial.

INDICATIONS AND USAGE

Metastatic Breast Cancer

Tamoxifen citrate is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, tamoxifen citrate is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from tamoxifen citrate therapy.

Adjuvant Treatment of Breast Cancer

Tamoxifen citrate is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. In some tamoxifen citrate adjuvant studies, most of the benefit to date has been in the subgroup with four or more positive axillary nodes.

Tamoxifen citrate is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.

The estrogen and progesterone receptor values may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial.

Tamoxifen citrate reduces the occurrence of contralateral breast cancer in patients receiving adjuvant tamoxifen citrate therapy for breast cancer.

Ductal Carcinoma in Situ (DCIS)

In women with DCIS, following breast surgery and radiation, tamoxifen citrate is indicated to reduce the risk of invasive breast cancer (see **BOXED WARNING** at the beginning of the label). The decision regarding therapy with tamoxifen for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen therapy.

Current data from clinical trials support five years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

Reduction in Breast Cancer Incidence in High Risk Women

Tamoxifen citrate is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. This effect was shown in a study of 5 years planned duration with a median follow-up of 4.2 years. Twenty-five percent of the participants received drug for 5 years. The longer term effects are not known. In this study, there was no impact of tamoxifen on overall or breast cancer-related mortality (see **BOXED WARNING** at the beginning of the label).

Tamoxifen citrate is indicated only for high-risk women. "High risk" is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer ≥ 1.67%, as calculated by the Gail Model.

Examples of combinations of factors predicting a 5-year risk ≥ 1.67% are:

Age 35 or older and any of the following combination of factors:

- One first degree relative with a history of breast cancer, 2 or more benign biopsies, and a history of a breast biopsy showing atypical hyperplasia; or
- At least 2 first degree relatives with a history of breast cancer, and a personal history of at least one breast biopsy; or
- LCIS

Age 40 or older and any of the following combination of factors:

- One first degree relative with a history of breast cancer, 2 or more benign biopsies, age at first live birth 25 or older, and age at menarche 11 or younger; or
- At least 2 first degree relatives with a history of breast cancer, and age at first live birth 19 or younger; or
- One first degree relative with a history of breast cancer, and a personal history of a breast biopsy showing atypical hyperplasia.

Age 45 or older and any of the following combination of factors:

- At least 2 first degree relatives with a history of breast cancer and age at first live birth 24 or younger; or
- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, age at menarche 11 or less and age at first live birth 20 or more.

Age 50 or older and any of the following combination of factors:

- At least 2 first degree relatives with a history of breast cancer; or
- History of one breast biopsy showing atypical hyperplasia, and age at first live birth 30 or older and age at menarche 11 or less; or
- History of at least two breast biopsies with a history of atypical hyperplasia, and age at first live birth 30 or more.

Age 55 or older and any of the following combination of factors:

- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, and age at menarche 11 or less; or
- History of at least 2 breast biopsies with a history of atypical hyperplasia, and age at first live birth 20 or older.

Age 60 or older and:

- 5-year predicted risk of breast cancer ≥ 1.67%, as calculated by the Gail Model.

For women whose risk factors are not described in the above examples, the Gail Model is necessary to estimate absolute breast cancer risk. Health Care Professionals can obtain a Gail Model Risk Assessment Tool by dialing 1-800-284-2480.

There are no data available regarding the effect of tamoxifen citrate on breast cancer incidence in women with inherited mutations (BRCA1, BRCA2).

After an assessment of the risk of developing breast cancer, the decision regarding therapy with tamoxifen citrate for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen citrate therapy. In the NSABP P-1 trial, tamoxifen citrate treatment lowered the risk of developing breast cancer during

the follow-up period of the trial, but did not eliminate breast cancer risk (See Table 3 in **CLINICAL PHARMACOLOGY).**

CONTRAINDICATIONS

Tamoxifen citrate tablets are contraindicated in patients with known hypersensitivity to the drug or any of its ingredients.

Reduction in Breast Cancer Incidence in High Risk Women and Women with DCIS
Tamoxifen is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep vein thrombosis or pulmonary embolus.

WARNINGS

Effects in Metastatic Breast Cancer Patients
As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with tamoxifen. If hypercalcemia does occur, appropriate measures should be taken and, if severe, tamoxifen should be discontinued.

Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma
An increased incidence of uterine malignancies has been reported in association with tamoxifen treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen. Most uterine malignancies seen in association with tamoxifen are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed mullerian tumors, have also been reported. Uterine sarcoma is generally associated with a higher FIGO stage (III/IV) at diagnosis, poorer prognosis, and shorter survival. Uterine sarcoma has been reported to occur more frequently among long-term users ($\geq$ 2 years) of tamoxifen than non-users. Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal.

In the NSABP P-1 trial, among participants randomized to tamoxifen there was a statistically significant increase in the incidence of endometrial cancer (33 cases of invasive endometrial cancer, compared to 14 cases among participants randomized to placebo (RR=2.48, 95% CI: 1.27-4.92). The 33 cases in participants receiving tamoxifen were FIGO Stage 1, including 20 IA, 12 1B, and 1 IC endometrial adenocarcinomas. In participants randomized to placebo, 13 were FIGO Stage I (8 IA and 5 IB) and 1 was FIGO Stage IV. Five women on tamoxifen and 1 on placebo received postoperative radiation therapy in addition to surgery. This increase was primarily observed among women at least 50 years of age at the time of randomization (26 cases of invasive endometrial cancer, compared to 6 cases among participants randomized to placebo (RR=4.50, 95% CI: 1.78-13.16). Among women $\leq$ 49 years of age at the time of randomization there were 7 cases of invasive endometrial cancer, compared to 8 cases among participants randomized to placebo (RR=0.94, 95% CI: 0.28-2.89). If age at the time of diagnosis is considered, there were 4 cases of endometrial cancer among participants $\leq$ 49 randomized to tamoxifen compared to 2 among participants randomized to placebo (RR=2.21, 95% CI: 0.4-12.0). For women $\geq$ 50 at the time of diagnosis, there were 29 cases among participants randomized to tamoxifen compared to 12 among women on placebo (RR=2.5, 95% CI: 1.3-4.9). The risk ratios were similar in the two groups, although fewer events occurred in younger women. Most (29 of 33 cases in the tamoxifen group) endometrial cancers were diagnosed in symptomatic women, although 5 of 33 cases in the tamoxifen group occurred in

asymptomatic women. Among women receiving tamoxifen the events appeared between 1 and 61 months (average=32 months) from the start of treatment.

In an updated review of long-term data (median length of total follow-up is 6.9 years, including blinded follow-up) on 8,306 women with an intact uterus at randomization in the NSABP P-1 risk reduction trial, the incidence of both adenocarcinomas and rare uterine sarcomas was increased in women taking tamoxifen. During blinded follow-up, there were 36 cases of FIGO Stage I endometrial adenocarcinoma (22 were FIGO Stage IA, 13 IB, and 1 IC) in women receiving tamoxifen and 15 cases in women receiving placebo [14 were FIGO Stage 1 (9 IA and 5 IB), and I case was FIGO Stage IV]. Of the patients receiving tamoxifen who developed endometrial cancer, one with Stage IA and 4 with Stage IB cancers received radiation therapy. In the placebo group, one patient with FIGO Stage 1B cancer received radiation therapy and the patient with FIGO Stage IVB cancer received chemotherapy and hormonal therapy. During total follow-up, endometrial adenocarcinoma was reported in 53 women randomized to tamoxifen (30 cases of FIGO Stage IA, 20 were Stage IB, 1 was Stage IC, and 2 were Stage IIIC), and 17 women randomized to placebo (9 cases were FIGO Stage IA, 6 were Stage IB, 1 was Stage IIIC, and 1 was Stage IVB) (incidence per 1,000 women-years of 2.20 and 0.71, respectively). Some patients received post-operative radiation therapy in addition to surgery. Uterine sarcomas were reported in 4 women randomized to tamoxifen (1 was FIGO IA, 1 was FIGO IB, 1 was FIGO IIA, and 1 was FIGO IIIC) and one patient randomized to placebo (FIGO 1A); incidence per 1,000 women-years of 0.17 and 0.04, respectively. Of the patients randomized to tamoxifen, the FIGO IA and IB cases were a MMMT and sarcoma, respectively; the FIGO II was a MMMT; and the FIGO III was a sarcoma; and the one patient randomized to placebo had a MMMT. A similar increased incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving tamoxifen in five other NSABP clinical trials.

Any patient receiving or who has previously received tamoxifen who reports abnormal vaginal bleeding should be promptly evaluated. Patients receiving or who have previously received tamoxifen should have annual gynecological examinations and they should promptly inform their physicians if they experience any abnormal gynecological symptoms, e.g., menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge, or pelvic pain or pressure.

In the P-1 trial, endometrial sampling did not alter the endometrial cancer detection rate compared to women who did not undergo endometrial sampling (0.6% with sampling, 0.5% without sampling) for women with an intact uterus. There are no data to suggest that routine endometrial sampling in asymptomatic women taking tamoxifen to reduce the incidence of breast cancer would be beneficial.

Non-Malignant Effects on the Uterus
An increased incidence of endometrial changes including hyperplasia and polyps have been reported in association with tamoxifen treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the estrogenic properties of tamoxifen.

There have been a few reports of endometriosis and uterine fibroids in women receiving tamoxifen. The underlying mechanism may be due to the partial estrogenic effect of tamoxifen. Ovarian cysts have also been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with tamoxifen.

Tamoxifen has been reported to cause menstrual irregularity or amenorrhea.

Thromboembolic Effects of Tamoxifen
There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during tamoxifen therapy. When tamoxifen is coadminstered with chemotherapy, there may be a further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of tamoxifen should be carefully considered in women with a history of thromboembolic events.

Data from the NSABP P-1 trial show that participants receiving tamoxifen without a history of pulmonary emboli (PE) had a statistically significant increase in pulmonary emboli (18-tamoxifen, 6-placebo, RR=3.01, 95% CI: 1.15-9.27). Three of the pulmonary emboli, all in the tamoxifen arm, were fatal. Eighty-seven percent of the cases of pulmonary embolism occurred in women at least 50 years of age at randomization. Among women receiving tamoxifen, the events appeared between 2 and 60 months (average = 27 months) from the start of treatment.

In this same population, a non-statistically significant increase in deep vein thrombosis (DVT) was seen in the tamoxifen group (30-tamoxifen, 19-placebo; RR=1.59, 95% CI: 0.86-2.98). The same increase in relative risk was seen in women ≤ 49 and in women ≥ 50, although fewer events occurred in younger women. Women with thromboembolic events were at risk for a second related event (7 out of 25 women on placebo, 5 out of 48 women on tamoxifen) and were at risk for complications of the event and its treatment (0/25 on placebo, 4/48 on tamoxifen). Among women receiving tamoxifen, deep vein thrombosis events occurred between 2 and 57 months (average=19 months) from the start of treatment.

There was a non-statistically significant increase in stroke among patients randomized to tamoxifen (24-placebo; 34-tamoxifen; RR=1.42; 95% CI 0.82-2.51). Six of the 24 strokes in the placebo group were considered hemorrhagic in origin and 10 of the 34 strokes in the tamoxifen group were categorized as hemorrhagic. Seventeen of the 34 strokes in the tamoxifen group were considered occlusive and 7 were considered to be of unknown etiology. Fourteen of the 24 strokes on the placebo arm were reported to be occlusive and 4 of unknown etiology. Among these strokes 3 strokes in the placebo group and 4 strokes in the tamoxifen group were fatal. Eighty-eight percent of the strokes occurred in women at least 50 years of age at the time of randomization. Among women receiving tamoxifen, the events occurred between 1 and 63 months (average = 30 months) from the start of treatment.

Effects on the Liver: Liver Cancer:
In the Swedish trial using adjuvant tamoxifen 40 mg/day for 2-5 years, 3 cases of liver cancer have been reported in the tamoxifen treated group vs. 1 case in the observation group (See **PRECAUTIONS,-Carcinogenesis**). In other clinical trials evaluating tamoxifen, no cases of liver cancer have been reported to date.

One case of liver cancer was reported in NSABP P-1 in a participant randomized to tamoxifen.

Effects on the Liver: Non-Malignant Effects
Tamoxifen has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases

the relationship to tamoxifen is uncertain. However, some positive rechallenges and dechallenges have been reported.

In the NSABP P-1 trial, few grade 3-4 changes in liver function (SGOT, SGPT, bilirubin, alkaline phosphatase) were observed (10 on placebo and 6 on tamoxifen). Serum lipids were not systematically collected.

Other Cancers
A number of second primary tumors, occurring at sites other than the endometrium, have been reported following the treatment of breast cancer with tamoxifen in clinical trials. Data from the NSABP B-14 and P-1 studies show no increase in other (non-uterine) cancers among patients receiving tamoxifen. Whether an increased risk for other (non-uterine) cancers is associated with tamoxifen is still uncertain and continues to be evaluated.

Effects on the Eye
Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving tamoxifen. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen.

In the NSABP P-1 trial, an increased risk of borderline significance of developing cataracts among those women without cataracts at baseline (540-tamoxifen; 483-placebo; RR=1.13, 95% CI: 1.00-1.28) was observed. Among these same women, tamoxifen was associated with an increased risk of having cataract surgery (101-tamoxifen; 63-placebo; RR=1.62, 95% CI 1.18-2.22) (See Table 3 in **CLINICAL PHARMACOLOGY**). Among all women on the trial (with or without cataracts at baseline), tamoxifen was associated with an increased risk of having cataract surgery (201- tamoxifen; 129-placebo; RR=1.58, 95% CI 1.26-1.97). Eye examinations were not required during the study. No other conclusions regarding non-cataract ophthalmic events can be made.

Pregnancy Category D
Tamoxifen may cause fetal harm when administered to a pregnant woman. Women should be advised not to become pregnant while taking tamoxifen or within 2 months of discontinuing tamoxifen and should use barrier or nonhormonal contraceptive measures if sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups when compared to historical controls. Several pregnant marmosets were dosed with 10 mg/kg/day (about 2-fold the daily maximum recommended human dose on a mg/m^2 basis) during organogenesis or in the last half of pregnancy. No deformations were seen and, although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations.

In rodent models of fetal reproductive tract development, tamoxifen (at doses 0.002 to 2.4-fold the daily maximum recommended human dose on a mg/m^2 basis) caused changes in both sexes that are similar to those caused by estradiol, ethynylestradiol and

diethylstilbestrol. Although the clinical relevance of these changes is unknown, some of these changes, especially vaginal adenosis, are similar to those seen in young women who were exposed to diethylstilbestrol in utero and who have a 1 in 1,000 risk of developing clear-cell adenocarcinoma of the vagina or cervix. To date, in utero exposure to tamoxifen has not been shown to cause vaginal adenosis, or clear-cell adenocarcinoma of the vagina or cervix, in young women. However, only a small number of young women have been exposed to tamoxifen in utero, and a smaller number have been followed long enough (to age 15-20) to determine whether vaginal or cervical neoplasia could occur as a result of this exposure.

There are no adequate and well-controlled trials of tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, or within approximately two months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long-term risk of a DES-like syndrome.

Reduction in Breast Cancer Incidence in High Risk Women - Pregnancy Category D
For sexually active women of child-bearing potential, tamoxifen therapy should be initiated during menstruation. In women with menstrual irregularity, a negative β-HCG immediately prior to the initiation of therapy is sufficient (See **PRECAUTIONS Information for Patients - Reduction in Breast Cancer Incidence in High Risk Women).**

PRECAUTIONS
General
Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking tamoxifen for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen; this can sometimes be severe.
In the NSABP P-1 trial, 6 women on tamoxifen and 2 on placebo experienced grade 3-4 drops in platelet count ($\leq$ 50, 000/mm^3).

Information for Patients
Patients should be instructed to read the Medication Guide supplied as required by law when tamoxifen citrate is dispensed. The complete text of the Medication Guide is reprinted at the end of this document.

Reduction in Invasive Breast Cancer and DCIS in Women with DCIS
Women with DCIS treated with lumpectomy and radiation therapy who are considering tamoxifen to reduce the incidence of a second breast cancer event should assess the risks and benefits of therapy, since treatment with tamoxifen decreased the incidence of invasive breast cancer, but has not been shown to affect survival (See Table 1 in **CLINICAL PHARMACOLOGY).**

Reduction in Breast Cancer Incidence in High Risk Women
Women who are at high risk for breast cancer can consider taking tamoxifen therapy to reduce the incidence of breast cancer. Whether the benefits of treatment are considered to outweigh the risks depends on a woman's personal health history and on how she weighs the

benefits and risks. Tamoxifen therapy to reduce the incidence of breast cancer may therefore not be appropriate for all women at high risk for breast cancer. Women who are considering tamoxifen therapy should consult their health care professional for an assessment of the potential benefits and risks prior to starting therapy for reduction in breast cancer incidence (See **Table 3** in **CLINICAL PHARMACOLOGY**). Women should understand that tamoxifen reduces the incidence of breast cancer, but may not eliminate risk. Tamoxifen decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors. In women with breast cancer who are at high risk of developing a second breast cancer, treatment with about 5 years of tamoxifen reduced the annual incidence rate of a second breast cancer by approximately 50%.

Women who are pregnant or who plan to become pregnant should not take tamoxifen to reduce her risk of breast cancer. Effective nonhormonal contraception must be used by all premenopausal women taking tamoxifen and for approximately two months after discontinuing therapy if they are sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. For sexually active women of child-bearing potential, tamoxifen therapy should be initiated during menstruation. In women with menstrual irregularity, a negative β-HCG immediately prior to the initiation of therapy is sufficient (See **WARNINGS-Pregnancy Category D**).

Two European trials of tamoxifen to reduce the risk of breast cancer were conducted and showed no difference in the number of breast cancer cases between the tamoxifen and placebo arms. These studies had trial designs that differed from that of NSABP P-1, were smaller than NSABP P-1, and enrolled women at a lower risk for breast cancer than those in P-1.

Monitoring During Tamoxifen Therapy
Women taking or having previously taken tamoxifen should be instructed to seek prompt medical attention for new breast lumps, vaginal bleeding, gynecologic symptoms (menstrual irregularities, changes in vaginal discharge, or pelvic pain or pressure), symptoms of leg swelling or tenderness, unexplained shortness of breath, or changes in vision. Women should inform all care providers, regardless of the reason for evaluation, that they take tamoxifen. Women taking tamoxifen to reduce the incidence of breast cancer should have a breast examination, a mammogram, and a gynecologic examination prior to the initiation of therapy. These studies should be repeated at regular intervals while on therapy, in keeping with good medical practice. Women taking tamoxifen as adjuvant breast cancer therapy should follow the same monitoring procedures as for women taking tamoxifen for the reduction in the incidence of breast cancer. Women taking tamoxifen as treatment for metastatic breast cancer should review this monitoring plan with their care provider and select the appropriate modalities and schedule of evaluation.

Laboratory Tests
Periodic complete blood counts, including platelet counts, and periodic liver function tests should be obtained.

Drug Interactions
When tamoxifen is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

In the NSABP P-1 trial, women who required coumarin-type anticoagulants for any reason were ineligible for participation in the trial (See **CONTRAINDICATIONS**).

There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with tamoxifen.

Tamoxifen reduced letrozole plasma concentrations by 37%. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases for activation, is not known. Tamoxifen and N-desmethyl tamoxifen plasma concentrations have been shown to be reduced when coadministered with rifampin or aminoglutethimide. Induction of CYP3A4-mediated metabolism is considered to be the mechanism by which these reductions occur; other CYP3A4 inducing agents have not been studied to confirm this effect.

One patient receiving tamoxifen with concomitant phenobarbital exhibited a steady state serum level of tamoxifen lower than that observed for other patients (i.e., 26 ng/mL vs. mean value of 122 ng/mL). However, the clinical significance of this finding is not known. Rifampin induced the metabolism of tamoxifen and significantly reduced the plasma concentrations of tamoxifen in 10 patients. Aminoglutethimide reduces tamoxifen and N-desmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen and N-desmethyl tamoxifen.

Drug/Laboratory Testing Interactions
During postmarketing surveillance, T4 elevations were reported for a few postmenopausal patients which may be explained by increases in thyroid-binding globulin. These elevations were not accompanied by clinical hyperthyroidism.

Variations in the karyopyknotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently seen in postmenopausal patients given tamoxifen.

In the postmarketing experience with tamoxifen, infrequent cases of hyperlipidemias have been reported. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with pre-existing hyperlipidemias (See **ADVERSE REACTIONS-Postmarketing experience** section).

Carcinogenesis
A conventional carcinogenesis study in rats at doses of 5, 20, and 35 mg/kg/day (about one, three and seven-fold the daily maximum recommended human dose on a mg/m^2 basis) administered by oral gavage for up to 2 years revealed a significant increase in hepatocellular carcinoma at all doses. The incidence of these tumors was significantly greater among rats administered 20 or 35 mg/kg/day (69%) compared to those administered 5 mg/kg/day (14%). In a separate study, rats were administered tamoxifen at 45 mg/kg/day (about nine-fold the daily maximum recommended human dose on a mg/m^2 basis); hepatocellular neoplasia was exhibited at 3 to 6 months.

Granulosa cell ovarian tumors and interstitial cell testicular tumors were observed in two separate mouse studies. The mice were administered the trans and racemic forms of

tamoxifen for 13 to 15 months at doses of 5, 20 and 50 mg/kg/day (about one-half, two and five-fold the daily recommended human dose on a mg/m^2 basis).

Mutagenesis
No genotoxic potential was found in a conventional battery of *in vivo* and *in vitro* tests with pro- and eukaryotic test systems with drug metabolizing systems. However, increased levels of DNA adducts were observed by ^{32}P post-labeling in DNA from rat liver and cultured human lymphocytes. Tamoxifen also has been found to increase levels of micronucleus formation *in vitro* in human lymphoblastoid cell line (MCL-5). Based on these findings, tamoxifen is genotoxic in rodent and human MCL-5 cells.

Impairment of Fertility
Tamoxifen produced impairment of fertility and conception in female rats at doses of 0.04 mg/kg/day (about 0.01-fold the daily maximum recommended human dose on a mg/m^2 basis) when dosed for two weeks prior to mating through day 7 of pregnancy. At this dose, fertility and reproductive indices were markedly reduced with total fetal mortality. Fetal mortality was also increased at doses of 0.16 mg/kg/day (about 0.03-fold the daily maximum recommended human dose on a mg/m^2 basis) when female rats were dosed from days 7-17 of pregnancy Tamoxifen produced abortion, premature delivery and fetal death in rabbits administered doses equal to or greater than 0.125 mg/kg/day (about 0.05-fold the daily maximum recommended human dose on a mg/m^2 basis). There were no teratogenic changes in either rats or rabbits.

Pregnancy Category D: See **WARNINGS**

Nursing Mothers

Tamoxifen has been reported to inhibit lactation. Two placebo-controlled studies in over 150 women have shown that tamoxifen significantly inhibits early postpartum milk production. In both studies tamoxifen was administered within 24 hours of delivery for between 5 and 18 days. The effect of tamoxifen on established milk production is not known.

There are no data that address whether tamoxifen is excreted into human milk. If excreted, there are no data regarding the effects of tamoxifen in breast milk on the breastfed infant or breastfed animals. However, direct neonatal exposure of tamoxifen to mice and rats (not via breast milk) produced 1) reproductive tract lesions in female rodents (similar to those seen in humans after intrauterine exposure to diethylstilbestrol) and 2) functional defects of the reproductive tract in male rodents such as testicular atrophy and arrest of spermatogenesis.

It is not known if tamoxifen is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tamoxifen, women taking tamoxifen should not breast feed.

Reduction in Breast Cancer Incidence in High Risk Women and Women with DCIS:
It is not known if tamoxifen is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tamoxifen, women taking tamoxifen should not breast feed.

Pediatric Use
The use of SOLTAMOX™ in pediatric patients has not been evaluated.

Geriatric Use
In the NSABP P-1 trial, the percentage of women at least 65 years of age was 16%. Women at least 70 years of age accounted for 6% of the participants. A reduction in breast cancer incidence was seen among participants in each of the subsets: A total of 28 and 10 invasive breast cancers were seen among participants 65 and older in the placebo and tamoxifen groups, respectively. Across all other outcomes, the results in this subset reflect the results observed in the subset of women at least 50 years of age. No overall differences in tolerability were observed between older and younger patients (See **CLINICAL PHARMACOLOGY - Clinical Studies - Reduction in Breast Cancer Incidence in High Risk Women** section).

In the NSABP B-24 trial, the percentage of women at least 65 years of age was 23%. Women at least 70 years of age accounted for 10% of participants. A total of 14 and 12 invasive breast cancers were seen among participants 65 and older in the placebo and tamoxifen groups, respectively. This subset is too small to reach any conclusions on efficacy. Across all other endpoints, the results in this subset were comparable to those of younger women enrolled in this trial. No overall differences in tolerability were observed between older and younger patients.

ADVERSE REACTIONS
Adverse reactions to tamoxifen are relatively mild and rarely severe enough to require discontinuation of treatment in breast cancer patients.

Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with tamoxifen as compared to placebo.

In one single-dose pharmacokinetic study in healthy perimenopausal and postmenopausal female volunteers, throat irritation was reported by 3 of 60 evaluable subjects (5.0%) in the Soltamox™ treatment groups while none of the subjects in the tamoxifen reference group reported this event. All events were mild and occurred within an hour after dosing. All events were resolved within 24 hours.

Metastatic Breast Cancer
Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting tamoxifen and generally subside rapidly.

In patients treated with tamoxifen for metastatic breast cancer, the most frequent adverse reaction to tamoxifen is hot flashes.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness, headache, hair thinning and/or partial hair loss, and vaginal dryness.

Premenopausal Women
The following table summarizes the incidence of adverse reactions reported at a frequency of 2% or greater from clinical trials (Ingle, Pritchard, Buchanan) which compared tamoxifen therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

Adverse Reactions*	TAMOXIFEN All Effects % of Women n =104	OVARIAN ABLATION All Effects % of Women n = 100
Flush	33	46
Amenorrhea	16	69
Altered Menses	13	5
Oligomenorrhea	9	1
Bone Pain	6	6
Menstrual Disorder	6	4
Nausea	5	4
Cough/Coughing	4	1
Edema	4	1
Fatigue	4	1
Musculoskeletal Pain	3	0
Pain	3	4
Ovarian Cyst(s)	3	2
Depression	2	2
Abdominal Cramps	1	2
Anorexia	1	2

*Some women had more than one adverse reaction.

Male Breast Cancer

Tamoxifen is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of tamoxifen in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

Adjuvant Breast Cancer

In the NSABP B-14 study, women with axillary node-negative breast cancer were randomized to 5 years of tamoxifen 20 mg/day or placebo following primary surgery. The reported adverse effects are tabulated below (mean follow-up of approximately 6.8 years) showing adverse events more common on tamoxifen than on placebo. The incidence of hot flashes (64% vs. 48%), vaginal discharge (30% vs. 15%), and irregular menses (25% vs. 19%) were higher with tamoxifen compared with placebo. All other adverse effects occurred with similar frequency in the 2 treatment groups, with the exception of thrombotic events; a higher incidence was seen in tamoxifen-treated patients (through 5 years, 1.7% vs. 0.4%). Two of the patients treated with tamoxifen who had thrombotic events died.

NSABP B-14 Study

	% of Women	
	TAMOXIFEN (n=1422)	Placebo (n=1437)
Hot Flashes	64	48
Fluid Retention	32	30
Vaginal Discharge	30	15
Nausea	26	24
Irregular Menses	25	19
Weight Loss (>5%)	23	18
Skin Changes	19	15
Increased SGOT	5	3
Increased Bilirubin	2	1
Increased Creatinine	2	1
Thrombocytopenia*	2	1
Thrombotic Events		
Deep Vein Thrombosis	0.8	0.2
Pulmonary Embolism	0.5	0.2
Superficial Phlebitis	0.4	0.0

*Defined as a platelet count of <100,000/mm^3

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, tamoxifen or placebo was administered for 2 years to women following mastectomy. When compared to placebo, tamoxifen showed a significantly higher incidence of hot flashes (19% vs. 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment groups with the exception of thrombocytopenia where the incidence for tamoxifen was 10% vs. 3% for placebo, an observation of borderline statistical significance.

In other adjuvant studies, Toronto and tamoxifen Adjuvant Trial Organization (NATO), women received either tamoxifen or no therapy. In the Toronto study, hot flashes were observed in 29% of patients for tamoxifen vs. 1% in the untreated group. In the NATO trial, hot flashes and vaginal bleeding were reported in 2.8% and 2.0% of women, respectively, for tamoxifen vs. 0.2% for each in the untreated group.

Ductal Carcinoma in Situ (DCIS)
The type and frequency of adverse events in the NSABP B-24 trial were consistent with those observed in the other adjuvant trials conducted with tamoxifen.

Reduction in Breast Cancer Incidence in High Risk Women
In the NSABP P-1 Trial, there was an increase in five serious adverse effects in the tamoxifen group: endometrial cancer (33 cases in the tamoxifen group vs. 14 in the placebo group); pulmonary embolism (18 cases in the tamoxifen group vs. 6 in the placebo group); deep vein thrombosis (30 cases in the tamoxifen group vs. 19 in the placebo group); stroke (34 cases in the tamoxifen group vs. 24 in the placebo group); cataract formation (540 cases in the tamoxifen group vs. 483 in the placebo group) and cataract surgery (101 cases in the tamoxifen group vs. 63 in the placebo group) (See **WARNINGS** and Table 3 in **CLINICAL PHARMACOLOGY).**

The following table presents the adverse events observed in NSABP P-1 by treatment arm. Only adverse events more common on tamoxifen than placebo are shown.

NSABP P-1 Trial: All Adverse Events

	% of Women	
	TAMOXIFEN (n=6681)	Placebo (n=6707)
Self Reported Symptoms	N=6441[1]	N=6469[1]
Hot Flashes	80	68
Vaginal Discharges	55	35
Vaginal Bleeding	23	22
Laboratory Abnormalities	N=6520[2]	N=6535[2]
Platelets decreased	0.7	0.3
Adverse Effects	N=6492[3]	N=6484[3]
Other Toxicities		
Mood	11.6	10.8
Infection/Sepsis	6.0	5.1
Constipation	4.4	3.2
Alopecia	5.2	4.4
Skin	5.6	4.7
Allergy	2.5	2.1

[1]Number with Quality of Life Questionnaires
[2]Number with Treatment Follow-up Forms
[3]Number with Adverse Drug Reaction Forms

In the NSABP P-1 trial, 15.0% and 9.7% of participants receiving tamoxifen and placebo therapy, respectively, withdrew from the trial for medical reasons. The following are the medical reasons for withdrawing from tamoxifen and placebo therapy, respectively: Hot flashes (3.1% vs. 1.5%) and Vaginal Discharge (0.5% vs. 0.1%).

In the NSABP P-1 trial, 8.7% and 9.6% of participants receiving tamoxifen and placebo therapy, respectively, withdrew for non-medical reasons.

On the NSABP P-1 trial, hot flashes of any severity occurred in 68% of women on placebo and in 80% of women on tamoxifen. Severe hot flashes occurred in 28% of women on placebo and 45% of women on tamoxifen. Vaginal discharge occurred in 35% and 55% of women on placebo and tamoxifen respectively; and was severe in 4.5% and 12.3% respectively. There was no difference in the incidence of vaginal bleeding between treatment arms.

Postmarketing Experience
Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities, skin rash and headaches. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment. Very rare reports of erythema multiforme, Stevens-Johnson syndrome, bullous pemphigoid, interstitial pneumonitis, and rare reports of hypersensitivity reactions including angioedema have been reported with tamoxifen therapy. In some of these cases, the time to onset was more than one year. Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen (see **PRECAUTIONS, Drug/Laboratory Testing Interactions** section).

OVERDOSAGE
Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions.

Acute overdosage in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of tamoxifen in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity

manifested by tremor, hyperreflexia, unsteady gait and dizziness were noted. These symptoms occurred within 3-5 days of beginning tamoxifen and cleared within 2-5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after tamoxifen was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to tamoxifen therapy is unknown. Doses given in these patients were all greater than 400 mg/m^2 loading dose, followed by maintenance doses of 150 mg/m^2 of tamoxifen given twice a day.

In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/m^2 loading dose, followed by maintenance doses of 80 mg/m^2 of tamoxifen given twice a day. For a woman with a body surface area of 1.5 m^2 the minimal loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 6 fold higher in respect to the maximum recommended dose.

No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening). A 20 mg dose of SOLTAMOX™ is administered as 10 mL (equivalent to 2 teaspoons) of the oral solution.

In three single agent adjuvant studies in women, one 10 mg tamoxifen citrate tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years. In the NSABP B-14 adjuvant study in women with node-negative breast cancer, one 10 mg tamoxifen citrate tablet was given twice a day for at least 5 years. Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit (see **CLINICAL PHARMACOLOGY**). In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy. There was no indication that doses greater than 20 mg per day were more effective. Current data from clinical trials support 5 years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

Ductal Carcinoma in Situ (DCIS)

The recommended dose is tamoxifen citrate 20 mg daily for 5 years.

Reduction in Breast Cancer Incidence in High Risk Women

The recommended dose is tamoxifen citrate 20 mg daily for 5 years. There are no data to support the use of tamoxifen citrate other than for 5 years (See **CLINICAL PHARMACOLOGY-Clinical Studies - Reduction in Breast Cancer Incidence in High Risk Women**).

HOW SUPPLIED

SOLTAMOX™ Oral Solution is a sugar-free, clear colorless liquid, with licorice and aniseed odor and taste. It is supplied in a 150mL bottle, each 5mL solution contains 15.2 mg tamoxifen citrate, equivalent to 10 mg tamoxifen. NDC (*# not available at this time*).
Do not store above 25° C (77° F). Store in the original package in order to protect from light. Use within 3 months of opening. Storage: DO NOT freeze or refrigerate.

R_X only Dated; 8/25/2005

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MEDICATION GUIDE

SOLTAMOX™ Oral Solution
(SOL-ta-mox)
Generic name: tamoxifen citrate

Written for women who use SOLTAMOX™ *to lower their high chance of getting breast cancer or who have ductal carcinoma in situ (DCIS)*

This Medication Guide discusses only the use of SOLTAMOX™ to lower the chance of getting breast cancer in high-risk women and in women treated for DCIS.

People taking SOLTAMOX™ **to treat** breast cancer have different benefits and different decisions to make than high-risk women or women with ductal carcinoma in situ (DCIS) taking SOLTAMOX™ to reduce the chance of getting breast cancer. If you already have breast cancer, talk with your doctor about how the benefits of treating breast cancer with SOLTAMOX™ compare to the risks that are described in this document.

Why should I read this Medication Guide?

This guide has information to help you decide whether to use SOLTAMOX™ to lower your chance of getting breast cancer.

You and your doctor should talk about whether the possible benefit of SOLTAMOX™ in lowering your high chance of getting breast cancer is greater than its possible risks. Your doctor has a special computer program or hand-held calculator to tell if you are in the high-risk group. If you have DCIS and have been treated with surgery and radiation therapy, your doctor may prescribe SOLTAMOX™ to decrease your chance of getting invasive (spreading) breast cancer.

Read this guide carefully before you start SOLTAMOX™. It is important to read the information you get each time you get more medicine. There may be something new. This guide does not tell you everything about SOLTAMOX™ and does **not** take the place of talking with your doctor. Only you and your doctor can determine if SOLTAMOX™ is right for you.

What is the most important information I should know about using SOLTAMOX™ to reduce the chance of getting breast cancer?

SOLTAMOX™ (tamoxifen citrate) is a prescription medicine that is like estrogen (female hormone) in some ways and different in other ways. In the breast, tamoxifen can block estrogen's effects. Because it does this, tamoxifen may block the growth of breast cancers that need estrogen to grow (cancers that are estrogen- or progesterone-receptor positive).

Tamoxifen citrate can lower the chance of getting breast cancer in women with a higher than normal chance of getting breast cancer in the next five years (high-risk women) and women with DCIS. **Because high-risk women don't have cancer yet, it is important to think carefully about whether the possible benefit of tamoxifen in lowering the chance of getting breast cancer is greater than its possible risks.**

This Medication Guide reviews the risks and benefits of using SOLTAMOX ™ to reduce the chance of getting breast cancer in high-risk women and women with DCIS. This guide does not discuss the special benefits and decisions for people who already have breast cancer.

Why do women and men use SOLTAMOX ™?

SOLTAMOX™ has more than one use. SOLTAMOX™ is used:

1. **to lower the chance** of getting breast cancer in women with a higher than normal chance of getting breast cancer in the next 5 years (high-risk women).
2. **to lower the chance** of getting invasive (spreading) breast cancer in women who had surgery and radiation for ductal carcinoma in situ (DCIS). DCIS means the cancer is only inside the milk ducts.
3. **to treat** breast cancer in women after they have finished early treatment. Early treatment can include surgery, radiation, and chemotherapy. Tamoxifen may keep the cancer from spreading to others parts of the body. It may also reduce the woman's chance of getting a new breast cancer.
4. in women and men, **to treat** breast cancer that has spread to other parts of the body (metastatic breast cancer).

This guide talks only about using SOLTAMOX™ to lower the chance of getting breast cancer (#1 and #2 above).

What are the benefits of SOLTAMOX™ to lower the chance of getting breast cancer in high-risk women and in women treated for DCIS?

A large US study looked at **high-risk women** and compared the ones who took tamoxifen for 5 years with others who took a pill without tamoxifen (placebo). High-risk women were defined as women who have a 1.7% or greater chance of getting breast cancer in the next 5 years, based on a special computer program. In this study:

- Out of every 1,000 high-risk women **who took a placebo**, each year about 7 got breast cancer.
- Out of every 1,000 high-risk women **who took tamoxifen**, each year about 4 got breast cancer.

The study showed that on average, high-risk women who took tamoxifen lowered their chances of getting breast cancer by 44%, from 7 in 1,000 to 4 in 1,000.

Another US study looked at **women with DCIS** and compared those who took tamoxifen for 5 years with others who took a placebo. In this study:

- Out of every 1,000 women with DCIS **who took placebo**, each year about 17 got breast cancer.
- Out of every 1,000 women with DCIS **who took tamoxifen**, each year about 10 got breast cancer.

The study showed that on average, women with DCIS who took tamoxifen lowered their chances of getting invasive (spreading) breast cancer by 43%, from 17 in 1,000 to 10 in 1,000.

These studies do not mean that taking SOLTAMOX™ will lower your personal chance of getting breast cancer. We do not know what the benefits will be for any one woman who takes SOLTAMOX™ to reduce her chance of getting breast cancer.

What are the risks of SOLTAMOX™?

In the studies described under "What are the benefits of SOLTAMOX™?, the high-risk women who took tamoxifen got certain side effects at a higher rate than those who took a placebo. **Some of these side effects can cause death.**

In one study, in women who still had their uterus

- Out of every 1,000 women who took a placebo, each year 1 got endometrial cancer (cancer of the lining of the uterus) and none got uterine sarcoma (cancer of the body of the uterus).
- Out of every 1,000 women who took tamoxifen, each year 2 got endometrial cancer and fewer than 1 got uterine sarcoma.

These results show that, on average, in high-risk women **who still had their uterus,** tamoxifen doubled the chance of getting endometrial cancer from 1 in 1,000 to 2 in 1,000, and it increased the chance of getting uterine sarcoma. **This does not mean that taking tamoxifen will double your personal chance of getting endometrial cancer or increase your chance of getting uterine sarcoma.** We do not know what this risk will be for any one woman. The risk is different for women who no longer have their uterus.

For all women in this study, taking tamoxifen increased the risk of having a blood clot in their lungs or veins, or of having a stroke. In some cases, women died from these effects.

Tamoxifen increased the risk of getting cataracts (clouding of the lens of the eye) or needing cataract surgery. (See "What are the possible side effects of SOLTAMOX™ for more details about side effects.)

What don't we know about taking SOLTAMOX™ to reduce the chance of getting breast cancer?

We don't know

- if tamoxifen lowers the chance of getting breast cancer in women who have abnormal breast cancer genes (BRCA1 and BRCA2)
- if taking tamoxifen for 5 years reduces the number of breast cancers a woman will get in her lifetime or if it only delays some breast cancers
- if tamoxifen helps a woman live longer
- the effects of taking tamoxifen with hormone replacement therapy (HRT), birth control pills, or androgens (male hormones)
- the benefits of taking tamoxifen if you are less than 35 years old

Studies are being done to learn more about the long-term benefits and risks of using tamoxifen to reduce the chance of getting breast cancer.

What are the possible side effects of SOLTAMOX™?

The most common side effect of tamoxifen is hot flashes. This is not a sign of a serious problem.

The next most common side effect is vaginal discharge. If the discharge is bloody, it could be a sign of a serious problem. [See "Changes in the lining (endometrium) or body of your uterus" below.]

Less common but serious side effects of tamoxifen are listed below. These can occur at any time. Call your doctor right away if you have any signs of side effects listed below:

- **Changes in the lining (endometrium) or body of your uterus.** These changes may mean serious problems are starting, including cancer of the uterus. The signs of changes in the uterus are:
  - Vaginal bleeding or bloody discharge that could be a rusty or brown color. You should call your doctor even if only a small amount of bleeding occurs.
  - Change in your monthly bleeding, such as in the amount or timing of bleeding or increased clotting.
  - Pain or pressure in your pelvis (below your belly button).

- **Blood clots in your veins or lungs.** These can cause serious problems, including death. You may get clots up to 2-3 months after you stop taking tamoxifen. The signs of blood clots are:
  - sudden chest pain, shortness of breath, coughing up blood
  - pain, tenderness, or swelling in one or both of your legs

- **Stroke.** Stroke can cause serious medical problems, including death. The signs of stroke are:
  - sudden weakness, tingling, or numbness in your face, arm or leg, especially on one side of your body
  - sudden confusion, trouble speaking or understanding
  - sudden trouble seeing in one or both eyes
  - sudden trouble walking, dizziness, loss of balance or coordination
  - sudden severe headache with no known cause

- **Cataracts or increased chance of needing cataract surgery.** The sign of these problems is slow blurring of your vision.

- **Liver problems, including jaundice.** The signs of liver problems include lack of appetite and yellowing of your skin or whites of your eyes.

Another less serious side effect that has been reported occasionally with SOLTAMOX™ is mild, temporary throat irritation. These are not all the possible side effects of tamoxifen. For a complete list, ask your doctor or pharmacist.

Who should not take SOLTAMOX™?

Do not take tamoxifen for any reason if you

- **Are pregnant or plan to become pregnant while taking tamoxifen or during the 2 months after you stop taking tamoxifen. Tamoxifen may harm your unborn baby.** It takes about 2 months to clear tamoxifen from your body. To be sure you are not pregnant, you can start taking tamoxifen while you are having your menstrual period. Or, you can take a pregnancy test to be sure you are not pregnant before you begin.
- **Are breast-feeding.** We do not know if tamoxifen can pass through your milk and harm your baby.
- **Have had an allergic reaction to tamoxifen or SOLTAMOX™** (the other name for tamoxifen), or to any of its inactive ingredients.

If you get pregnant while taking SOLTAMOX™, stop taking it right away and contact your doctor. SOLTAMOX™ may harm your unborn baby.

Do not take SOLTAMOX™ to lower your chance of getting breast cancer if

- You ever had a blood clot that needed medical treatment.
- You are taking medicines to thin your blood, like warfarin, (also called Coumadin®*).
- Your ability to move around is limited for most of your waking hours.
- You are at risk for blood clots. Your doctor can tell you if you are at high risk for blood clots.
- You do not have a higher than normal chance of getting breast cancer. Your doctor can tell you if you are a high-risk woman.

How should I take SOLTAMOX™?

- Take 2 tsp SOLTAMOX™ once or twice a day, as directed by your physician. You can take SOLTAMOX™ with or without food. Take your medicine every day. It may be easier to remember if you take it at the same time each day.
- If you forget a dose, take it when you remember, then take the next dose as usual. If it is almost time for your next dose or you remember at your next dose, do not take more than 2 tsp at one time to make up a missed dose.
- Take SOLTAMOX™ for 5 years, unless your doctor tells you otherwise.

What should I avoid while taking SOLTAMOX™?

- **Do not become pregnant while taking tamoxifen or for 2 months after you stop.** Tamoxifen can stop hormonal birth control methods from working. Hormonal methods include birth control pills, patches, injections, rings and implants. Therefore, while taking tamoxifen, **use birth control methods that**

don't use hormones, such as condoms, diaphragms with spermicide, or plain IUD's. If you get pregnant, stop taking tamoxifen right away and call your doctor.

- **Do not breast feed.** We do not know if tamoxifen can pass through your milk and if it can harm the baby.

What should I do while taking SOLTAMOX™?

- Have regular gynecology check-ups ("female exams"), breast exams and mammograms. Your doctor will tell you how often. These will check for signs of breast cancer and cancer of the endometrium (lining of the uterus). Because tamoxifen does not prevent all breast cancers, and you may get other types of cancers, you need these exams to find any cancers as early as possible.
- Because tamoxifen can cause serious side effects, pay close attention to your body. Signs you should look for are listed in "What are the possible side effects of SOLTAMOX™"

- Tell all of the doctors that you see that you are taking SOLTAMOX™.
- Tell your doctor right away if you have any new breast lumps.

General information about the safe and effective use of SOLTAMOX™

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Your doctor has prescribed SOLTAMOX™ only for you. Do not give it to other people, even if they have a similar condition, because it may harm them. Do not use it for a condition for which it was not prescribed.

This Medication Guide is a summary of information about SOLTAMOX™ for women who use SOLTAMOX™ to lower their high chance of getting breast cancer or who have DCIS. If you want more information about SOLTAMOX™, ask your doctor or pharmacist. They can give you information about SOLTAMOX™ that is written for health professionals. For more information about SOLTAMOX™ or breast cancer, please visit www.savientpharma.com or call 1-866-692-6374.

Ingredients: tamoxifen, ethanol, glycerol, propylene glycol, sorbitol solution, licorice flavor, aniseed flavor, purified water.

*Coumadin@ is a registered trademark of Bristol-Myers Squibb Pharmaceuticals.

Savient Pharmaceuticals, Inc., East Brunswick, NJ 08816 Rev xx-0x

This Medication Guide has been approved by the U.S. Food and Drug Administration

SAVIENT PHARMACEUTICALS, INC.

One Tower Center, 14th Floor
East Brunswick, NJ 08816

SOLTAMOX™

TAMOXIFEN CITRATE

Oral Solution

(equivalent to)

10mg/5mL

Tamoxifen

New Drug Application [505(b)(2)]

Section 2

Labeling

Application Number:	**21-807**
Pharmacologic category:	A Nonsteroidal Antiestrogen
Product Name:	Soltamox™
Indication:	Treatment of Breast Cancer
Document status:	Draft
Document date:	XX XX 2004
Number of pages:	XX

Each 5mL dose of oral solution contains Tamoxifen Citrate USP 15.2mg (equivalent to 10mg tamoxifen). The product also contains ethanol (19% v/v), glycerol, propylene glycol, sorbitol solution, licorice and aniseed flavors and purified water. **Storage:** Store at Controlled Room Temperature 15° – 25 ° C (59 ° - 77° F). Store in original package in order to protect from light. Use within 3 months of opening. **Pharmacist:** Dispense only in original container with calibrated cup. BARCODE	**NDC#** **SOLTAMOX™** **TAMOXIFEN CITRATE** **Oral Solution** **(equivalent to)** **10mg/5mL** **Tamoxifen** **Rx Only** Sugar Free **150 mL** PATIENT PACK SAVIENT PHARMACEUTICALS, INC	KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN. **Dosage:** As prescribed by the physician. To be taken orally. See Package Insert for Complete Prescribing Information. Manufactured by: Rosemont Pharmaceuticals Ltd., Yorkdale Industrial Park, Braithwaite Street Leeds, LS11 9XE, UK Manufactured for: Savient Pharmaceuticals, Inc. East Brunswick, NJ 08816, USA LOT : MFG : EXP :

DRAFT CONTAINER LABEL

Lot:
Mfg:
Exp:

TAMOXIFEN CITRATE
Oral Solution
(equivalent to)
10mg/5mL
Tamoxifen

Rx only

SUGAR FREE

NDC#

SUGAR FREE

SOLTAMOX™

TAMOXIFEN CITRATE

Oral Solution

(equivalent to)

10mg/5 mL

Tamoxifen

Rx only

150 mL

Patient pack

SAVIENT PHARMACEUTICALS, INC

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(equivalent to)

10mg/5mL

Tamoxifen

Rx only

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Patient Pack

SAVIENT PHARMACEUTICALS, INC

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Dosage: As prescribed by the physician. To be taken orally.

See Package Insert for Complete Prescribing Information.

Manufactured by:
Rosemont Pharmaceuticals Ltd.,
Yorkdale Industrial Park, Braithwaite Street
Leeds, LS11 9XE, UK

Manufactured for:
Savient Pharmaceuticals, Inc.
East Brunswick, NJ 08816, USA

DRAFT CARTON LABEL

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/s/

Robert Justice
10/29/2005 04:36:30 PM

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US006127425A

United States Patent [19]

Tully

[11] Patent Number: 6,127,425

[45] Date of Patent: *Oct. 3, 2000

[54] ORAL LIQUID MEDICINE SOLUTION

[75] Inventor: Roger Edward Tully, Ilkley, United Kingdom

[73] Assignee: Akzo Nobel N.V., Arnhem, Netherlands

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: 09/106,172

[22] Filed: Jun. 26, 1998

[30] Foreign Application Priority Data

Jun. 27, 1997 [EP] European Pat. Off. 97201964

[51] Int. Cl.[7] A01N 33/02; A61K 31/135

[52] U.S. Cl. 514/648; 514/651; 568/328

[58] Field of Search 514/648, 651; 564/324

[56] References Cited

U.S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

240131	10/1987	European Pat. Off. .
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Primary Examiner—Frederick Krass

Attorney, Agent, or Firm—Mary E. Gormley

[57] ABSTRACT

Found is a pharmaceutical preparation which provides Tamoxifen Citrate in a liquid dosage form, viz. as an oral solution. The finding is based on a solvent comprising the following components: (a) of from 10% to 20% by weight of ethanol, (b) of from 10% to 60% by weight of a glycol; and (c) water, optionally containing additives, in a volume percentage adding up to 100% by volume. A preferred additive is sorbitol.

11 Claims, No Drawings

ORAL LIQUID MEDICINE SOLUTION

FIELD OF THE INVENTION

The invention is in the field of pharmaceutical compositions comprising, as a medicinally active ingredient, Tamoxifen. Tamoxifen is known as a medicine for the treatment of breast cancer and anovulatory infertility.

BACKGROUND OF THE INVENTION

Pharmaceutical preparations which provide a dosage form of Tamoxifen are known the dosage form being solid, viz. tablets having strengths of the medicinally active ingredient of from 10 mg Tamoxifen. The Tamoxifen regularly is present in the form of the corresponding citrate, ethanamine, 2-4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-(Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1), the IUPAC name of which is (Z)-2-[4-(1,2)-Diohenylbut-1-enyl) phenoxy]ethyldimethylamine citrate.

Although the known tablets are generally acceptable as far as their medicinal activity is concerned, the solid dosage form imposes restrictions on the pharmaceutical use of Tamoxifen. Some patient populations have a difficulty, physical or psychological, in swallowing solid dosage forms. If a liquid dosage form were available, these patients could more easily take the required dose of Tamoxifen, having it administered in the form of an oral liquid preparation or, e.g., by means of a naso-gastric tube.

However, such oral liquid preparations of Tamoxifen are neither available on the market, nor even known in the art. To manufacture a liquid preparation of Tamoxifen presents a problem to the person skilled in the art, as the compound has a poor solubility in pharmaceutically acceptable solvents and in view of the general difficulty in predicting the solubility of specific pharmaceutical salts such as Tamoxifen Citrate in any given liquid.

SUMMARY OF THE INVENTION

Hence, it is an object of the present invention to provide a liquid capable of dissolving Tamoxifen Citrate in a sufficiently high concentration. It is particularly desired to provide a solution of Tamoxifen Citrate in which the concentration of Tamoxifen is high enough to correspond to the concentration of the regular Tamoxifen tablets. A further object of the invention, is to find a method of dissolving Tamoxifen Citrate without chemically altering it, i.e., the use of known, solubility-enhancing, complexing agents is not preferred according to the invention.

Without detracting from the theoretical possibility that the Tamoxifen is present in another form, it will as a rule be the above-identified citrate. A further problem that may be incurred with this compound, is that its crystals exist in two polymorphic forms. The normally available compound is present as the meta stable polymorph. On crystallisation from protic solvents, the compound forms crystals of the stable polymorph. The stable polymorph exhibits undesirable characteristics, int.al., even further reduced solubility. These undesirable characteristics may affect the absorption behaviour in vivo, thereby reducing the bioavailability of the compound. The presence of these polymorphic forms precludes the formulation of Tamoxifen Citrate as a suspension. For, even with the low intrinsic solubility of the molecule, a small amount would enter (aqueous) solution and then leave it, crystallising in the less desirable polymorphic form. Hence, it is a further object of the invention to provide a liquid formulation of Tamoxifen Citrate where crystallisation will not occur.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a liquid mixture satisfying the above demands. Thus according to the present invention Tamoxifen is provided in a novel dosage form, viz. as a solution of at least approximately 1.5 mg/ml, and preferably of from 3 to approximately 6 mg/ml.

The possibility of providing Tamoxifen in the form of an oral solution can be considered a new and surprising achievement per se. It is particularly the determination of a suitable solvent combination which overcomes the technical problem of providing a Tamoxifen Citrate solution of sufficiently high concentration. The solvent system in accordance with the invention comprises the following components:

(a) from 10% to 20% by weight of ethanol,

(b) from 10% to 60% by weight of glycol; and

(c) water in a volume percentage adding up to 100% by volume.

Incidentally, in DD 293 263 it has been disclosed to mix tamoxifen with a minor amount of ethanol and polyethylene glycol, but this does not yield a solution.

The ethanol component (a) preferably is employed in about 15% by weight. If less than about 10% is used, the desired physical stability of the solution may be jeopardised, e.g. undesired crystallisation may occur upon storage at low (2–8° C.) temperatures. The upper limit is mainly determined by practical reasons. Too high a percentage of ethanol is undesirable in view of the flammability hazards during processing and the potential for evaporative losses during manufacture. Ethanol has a very discernible effect on taste perceptions when present at concentrations in excess of 20%. Hence, it is generally desired to keep ethanol concentrations as low as possible. The present invention allows using a relatively loss concentration of ethanol.

For the sake of obtaining a chemically stable formulation, the glycol component (b) may, in principle, consist of any (poly) glycol, e.g. polyethylene glycol of varying molecular weights, but for the desired organoleptic characteristics, i.e. mouthfeel and flavour, it is preferred for the glycol to be a low molecular weight glycol or glycerol. The low molecular weight glycol preferably is propylene glycol, glycerol, or a mixture thereof. If propylene glycol is employed, the preferred percentage thereof is about 10% by weight. If the percentage is decreased, care should be taken to maintain a physically stable solution. Due to the burning taste displayed by propylene glycol, too high a percentage thereof should preferably be avoided. If glycerol is employed, the percentage thereof preferably is about 40% to 50% by weight. The percentage may be increased, but care should be taken that the resulting formulation does not become too viscous for processing. The percentage may also be decreased, but in view of the relative increase of the amount of water, care should be taken that the Tamoxifen Citrate still dissolves to a sufficient extent. It is preferred for the glycol component (b) to consist of a mixture of about 10% by weight of propylene glycol and of from about 40% to 50% by weight of glycerol.

The water component (c) may comprise any suitable, conventional additive, such as flavours, sweeteners, and colouring agents. Particularly preferred additives are bulk-sweetening agents such as sucrose, or any other sugar, hydrogenated glucose, or any other modified sugar, or—most preferably—sorbitol. The sugars may be added as dry powders or, preferably, as solutions. The preferred sorbitol solution is a non-crystallising solution containing 70% by weight of sorbitol. In all cases care should be taken

that the resulting aqueous solution is still processable. In this respect, sorbitol preferably is employed in an aqueous solution of from 15% to 25% by weight, and most preferably about 20% by weight.

Within the teaching of the present invention, the person of ordinary skill in the art is capable, of taking the required care to provide, without undue experimentation, a solution on the basis of the above components (a) through (c) which, on the one hand has sufficient stability and, on the other hand does not have such a high viscosity as to become unworkable.

In terms of a solution which is the most stable, allows the dissolution of a relatively high percentage of Tamoxifen Citrate, and which maintains ease of processing, the most preferred formulation is a solvent mixture comprising 15% by weight of ethanol, 10% by weight of propylene glycol, 50% by weight of glycerol, and 20% by weight of a sorbitol solution, the remainder being water to the required volume. The formulation according to the invention provides a physically and chemically stable solution of Tamoxifen Citrate at the requited concentration.

The solution of the invention can be prepared by first making a mixture of the ethanol and glycol components, and then adding, generally under stirring, the required quantity of Tamoxifen Citrate. After complete dissolution, if present the optional ingredients, such as sorbitol and flavours, and water are added. According to the invention another method was found to be the following. First, Tamoxifen Citrate, in the desired quantity, is pre-dispersed in the glycol component, and then ethanol is added to complete dissolution. After dissolution, the remaining components are added, as explained above. This method is highly efficient, and therefore preferred, in the case of a glycol component that consists of a mixture of propylene glycol and glycerol. In that case, the Tamoxifen Citrate is first dispersed in the propylene glycol, using any conventional dispersion technique but, preferably, high shear mixing. The dispersion is added to the glycerol and, on addition, of the ethanol component, generally under stirring, a complete solution is rapidly achieved.

The invention will be further explained hereinafter with reference to the Examples.

EXAMPLES I

A quantity of 3.04 g of micronised Tamoxifen Citrate is dispersed, using high shear mixing, in 100.00 g of propylene glycol. The resulting dispersion is added to 450.00 g of glycerol and mixed to produce a homogeneous suspension. Then 150.00 g of ethanol is added and the mixture is stirred until a clear, bright, colourless solution is obtained. Subsequently, 200.00 g of a 70% by weight solution of sorbitol is added, as well as 2.00 g of flavours. Upon stirring, sufficient water is added to make to a volume of 1000 ml. Thus, a stable formulation of dissolved Tamoxifen Citrate is obtained.

EXAMPLE OF COMPARISON

In this Example, a comparison is made of several solvents and solvent combinations as to their capacity of dissolving Tamoxifen Citrate. The solutions are made by first mixing the solvent (components) and then adding Tamoxifen Citrate. Each time the maximum quantity of Tamoxifen Citrate is determined at which the solution is still stable. The results are outlined in the following table. The percentages given are all % by weight.

TABLE

Solvent components	Solubility (mg/ml)	Suitable?
water	0.165	no
5% of ethanol in water	0.283	no
10% of ethanol in water	0.424	no
15% of ethanol in water	0.666	no
5% of propylene glycol and 5% of ethanol in water	0.324	no
5% of propylene glycol and 10% of ethanol in water	0.761	no
5% of propylene glycol and 15% of ethanol in water	0.831	no
10% of propylene glycol, 10% of ethanol, and 0.3% of polysorbate 80 in water	1.47	just
10% of ethanol, 50% of glycerol and 20% of sorbitol solution in water	3.007	yes
10% of ethanol, 10% of propylene glycol, 50% of glycerol, and 20% of sorbitol solution in water	3.5	well
15% of ethanol, 10% of propylene glycol, 50% of glycerol, 20% of sorbitol solution in water	6.0	excellently

I claim:

1. A pharmaceutical preparation which provides a dosage form of Tamoxifen, wherein the dosage form comprises at least 1.5 mg/ml of Tamoxifen Citrate, in the absence of a complexing agent, in a pharmaceutically acceptable solution which is administered orally.

2. A pharmaceutical preparation according to claim 1, wherein the solution comprises a solvent comprising the following components: (a) from about 10% to 20% by weight of ethanol; (b) from about 10% to 60% by weight of glycol; and (c) water in a volume percentage adding up to 100% by volume.

3. A pharmaceutical preparation according to claim 2, wherein the glycol component is a mixture of propylene glycol and glycerol.

4. A pharmaceutical preparation according to claim 3, wherein the water component (c) contains a bulk-sweetening agent.

5. A pharmaceutical preparation according to claim 4, wherein the bulk-sweetening agent is from 15% to 25% by weight of sorbitol.

6. A pharmaceutical preparation according to claim 5, wherein the solvent comprises the following components: 15% by weight of ethanol, 10% by weight of propylene glycol, 50% by weight of glycerol, 20% by weight of a solution of 70% by weight of sorbitol in water, and water in a volume percentage adding up to 100% by volume.

7. A process for the preparation of the solution according to claim 2, comprising dissolving the Tamoxifen Citrate in a mixture of the ethanol and glycol components, and then adding the water component and any other additives.

8. A process for the preparation of a solution according to claim 2, comprising the steps of first dispersing Tamoxifen Citrate in the glycol component and then adding the ethanol component and the water component.

9. A process for the preparation of a solution in accordance with claim 3, comprising dispersing Tamoxifen Citrate in the propylene glycol to form a dispersion, adding the dispersion to the glycerol, then adding the ethanol component thereto to form a solution, and then adding the water component.

10. A pharmaceutical preparation according to claim 2, wherein the water component (c) contains additive(s) selected from the group consisting of flavors, sweeteners, and coloring agents.

11. A process according to claim 9, wherein the water component contains additive(s) selected from the group consisting of flavors, sweeteners and coloring agents.

* * * * *

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If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
6,127,425	**$910.00**	**$0.00**	**09/106,172**	**10/03/00**	**06/26/98**	**04**	**NO**	**PAID**	**0/97293US**

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PTO/SB/96 (09-04)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Savient Pharmaceuticals, Inc.

Application No./Patent No.: 6,127,425 Filed/Issue Date: October 3, 2000

Entitled: Oral Liquid Medicine Solution

Savient Pharmaceuticals, Inc., a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

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The document was recorded in the United States Patent and Trademark Office at
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The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

_____ 12/6/05
Signature Date

Philip K. Yachmetz (732) 565-4705
Printed or Typed Name Telephone Number

Senior Vice President, Corporate Strategy and General Counsel
Title

E

PTO/SB/81 (04-05)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	09/106,172
Filing Date	6/26/98
First Named Inventor	Tully
Title	ORAL LIQUID MEDICINE SOLUTION
Art Unit	1614
Examiner Name	Frederick Krass
Attorney Docket Number	ROS1997-0601-US

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I hereby appoint:

☑ Practitioners associated with the Customer Number: 49432

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I am the:

☐ Applicant/Inventor.

☑ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature		Date	12/6/05
Name	Philip K. Yachmetz	Telephone	(732) 565-4705
Title and Company	Senior Vice President, Corporate Strategy and General Counsel		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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